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Inhaled magnesium sulfate in the treatment of acute asthma (Review)

Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, Powell C

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Inhaled magnesium sulfate in the treatment of acute asthma.
Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD003898.
DOI: 10.1002/14651858.CD003898.pub6.

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[Intervention Review]

Inhaled magnesium sulfate in the treatment of acute asthma

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Editorial group: Cochrane Airways Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 11, 2017.

Citation: Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, Powell C. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No.: CD003898. DOI: 10.1002/14651858.CD003898.pub6.

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ABSTRACT

Background

Asthma exacerbations can be frequent and range in severity from mild to life-threatening. The use of magnesium sulfate ($MgSO_4$) is one of numerous treatment options available during acute exacerbations. While the efficacy of intravenous $MgSO_4$ has been demonstrated, the role of inhaled $MgSO_4$ is less clear.

Objectives

To determine the efficacy and safety of inhaled $MgSO_4$ administered in acute asthma.

Specific aims: to quantify the effects of inhaled $MgSO_4$ I) in addition to combination treatment with inhaled β_2-agonist and ipratropium bromide; ii) in addition to inhaled β_2-agonist; and iii) in comparison to inhaled β_2-agonist.

Search methods

We identified randomised controlled trials (RCTs) from the Cochrane Airways Group register of trials and online trials registries in September 2017. We supplemented these with searches of the reference lists of published studies and by contact with trialists.

Selection criteria

RCTs including adults or children with acute asthma were eligible for inclusion in the review. We included studies if patients were treated with nebulised $MgSO_4$ alone or in combination with β_2-agonist or ipratropium bromide or both, and were compared with the same co-intervention alone or inactive control.

Data collection and analysis

Two review authors independently assessed trial selection, data extraction and risk of bias. We made efforts to collect missing data from authors. We present results, with their 95% confidence intervals (CIs), as mean differences (MDs) or standardised mean differences (SMDs) for pulmonary function, clinical severity scores and vital signs; and risk ratios (RRs) for hospital admission. We used risk differences (RDs) to analyse adverse events because events were rare.

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Main results

Twenty-five trials (43 references) of varying methodological quality were eligible; they included 2907 randomised patients (2777 patients completed). Nine of the 25 included studies involved adults; four included adult and paediatric patients; eight studies enrolled paediatric patients; and in the remaining four studies the age of participants was not stated. The design, definitions, intervention and outcomes were different in all 25 studies; this heterogeneity made direct comparisons difficult. The quality of the evidence presented ranged from high to very low, with most outcomes graded as low or very low. This was largely due to concerns about the methodological quality of the included studies and imprecision in the pooled effect estimates.

Inhaled magnesium sulfate in addition to inhaled β_2-agonist and ipratropium

We included seven studies in this comparison. Although some individual studies reported improvement in lung function indices favouring the intervention group, results were inconsistent overall and the largest study reporting this outcome found no between-group difference at 60 minutes (MD −0.3 % predicted peak expiratory flow rate (PEFR), 95% CI −2.71% to 2.11%). Admissions to hospital at initial presentation may be reduced by the addition of inhaled magnesium sulfate (RR 0.95, 95% CI 0.91 to 1.00; participants = 1308; studies = 4; I^2 = 52%) but no difference was detected for re-admissions or escalation of care to ITU/HDU. Serious adverse events during admission were rare. There was no difference between groups for all adverse events during admission (RD 0.01, 95% CI −0.03 to 0.05; participants = 1197; studies = 2).

Inhaled magnesium sulfate in addition to inhaled β_2-agonist

We included 13 studies in this comparison. Although some individual studies reported improvement in lung function indices favouring the intervention group, none of the pooled results showed a conclusive benefit as measured by FEV1 or PEFR. Pooled results for hospital admission showed a point estimate that favoured the combination of $MgSO_4$ and β_2-agonist, but the confidence interval includes the possibility of admissions increasing in the intervention group (RR 0.78, 95% CI 0.52 to 1.15; participants = 375; studies = 6; I^2 = 0%). There were no serious adverse events reported by any of the included studies and no between-group difference for all adverse events (RD −0.01, 95% CI −0.05 to 0.03; participants = 694; studies = 5).

Inhaled magnesium sulfate versus inhaled β_2-agonist

We included four studies in this comparison. The evidence for the efficacy of β_2-agonists in acute asthma is well-established and therefore this could be considered a historical comparison. Two studies reported a benefit of β_2-agonist over $MgSO_4$ alone for PEFR and two studies reported no difference; we did not pool these results. Admissions to hospital were only reported by one small study and events were rare, leading to an uncertain result. No serious adverse events were reported in any of the studies in this comparison; one small study reported mild to moderate adverse events but the result is imprecise.

Authors' conclusions

Treatment with nebulised $MgSO_4$ may result in modest additional benefits for lung function and hospital admission when added to inhaled β_2-agonists and ipratropium bromide, but our confidence in the evidence is low and there remains substantial uncertainty. The recent large, well-designed trials have generally not demonstrated clinically important benefits. Nebulised $MgSO_4$ does not appear to be associated with an increase in serious adverse events. Individual studies suggest that those with more severe attacks and attacks of shorter duration may experience a greater benefit but further research into subgroups is warranted.

Despite including 24 trials in this review update we were unable to pool data for all outcomes of interest and this has limited the strength of the conclusions reached. A core outcomes set for studies in acute asthma is needed. This is particularly important in paediatric studies where measuring lung function at the time of an exacerbation may not be possible. Placebo-controlled trials in patients not responding to standard maximal treatment, including inhaled β_2-agonists and ipratropium bromide and systemic steroids, may help establish if nebulised $MgSO_4$ has a role in acute asthma. However, the accumulating evidence suggests that a substantial benefit may be unlikely.

PLAIN LANGUAGE SUMMARY

Is inhaled magnesium sulfate a safe and effective treatment for people with asthma attacks?

Background

Asthma attacks are common in adults and children. People having an attack may need to be treated in a hospital emergency department (A&E). Even with the best treatment, some people need to be admitted to hospital or even into the intensive care unit. Some guidelines suggest that giving magnesium sulfate, either by injection or inhaled straight into the lungs, may be beneficial. In this review we focused on inhaled (or 'nebulised') magnesium sulfate. We were particularly interested in finding out the effects of magnesium sulfate on lung function (breathing tests), severity scores and hospital admissions. We also wanted to know if it was safe.

Study characteristics

We looked for studies in adults and children attending the emergency department with an asthma attack. We included studies which compared giving inhaled magnesium sulfate, plus standard treatment, with standard treatment alone. We also included studies that

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compared inhaled magnesium sulfate directly with standard treatment. We included studies carried out anywhere in the world, at any time and written in any language.

Key results

We found 25 studies in total, which included nearly 3000 people with asthma attacks. This latest update of the review includes several large trials that were carried out to a very high standard. We found that adding inhaled magnesium sulfate to standard treatments may result in small benefits in terms of lung function, hospital admission and severity scores, but we are uncertain about these findings. This is because many of the studies were carried out in different ways and measured different outcomes at different times so it was quite hard to combine the results from individual studies. Inhaled magnesium sulfate did not seem to cause any serious side effects in the studies we found. We did not find evidence that using inhaled magnesium sulfate *instead* of standard treatment is beneficial.

Quality of the evidence

We used a scoring system to rate how confident we are in the findings presented. Our scores ranged from high confidence to very low confidence, but most outcomes we rated as low or very low. This is because we had concerns about the way in which some of the studies were carried out: for example, it was perhaps not clear how people were chosen for the two different treatment groups in the study; or it was unclear whether the patients or people running the trial knew who was getting which treatment. Another factor that reduced our confidence was uncertainty about the combined results: for example in some cases we could not tell whether magnesium sulfate was better, worse or the same.

Key message

There is some limited evidence that inhaled magnesium sulfate may have a small benefit for people having asthma attacks when added to standard treatment. However, the most recent, high-quality trials did not generally show important benefits. Also, we cannot be sure if some groups may benefit more than other, for example those having more severe attacks.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. MgSO4 + SABA + ipratropium compared to SABA + ipratropium in the treatment of acute asthma

$MgSO_4$+ SABA + ipratropium compared to SABA + ipratropium in the treatment of acute asthma

Patient or population: adults and children with acute exacerbation of asthma
Setting: emergency department/inpatient
Intervention: $MgSO_4$ + SABA + ipratropium
Comparison: SABA + ipratropium

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with SABA + ipratropium	Risk with MgSO4 + SABA + ipratropium				
Pulmonary function (% predicted FEV1) (90 to 120 minutes)	The mean pulmonary function (% predicted FEV1) was 65%	% predicted FEV1 was 3.28% higher (1.06 higher to 5.49 higher)	-	120 (2 RCTs)	⊕⊝⊝⊝ VERY LOW [1 2 3]	Outcome measured at 90 mins in 1 study and 120 mins in the other. 1 study (Gaur 2008) has reported much smaller standard deviations and contributes almost 90% of analysis weight
Pulmonary function % predicted PEF (60 minutes)	The mean pulmonary function % predicted PEF was 50.45%	% predicted PEF was 0.05 higher (2.33 lower to 2.42 higher)	-	636 (2 RCTs)	⊕⊕⊕⊝ MODERATE [2 4 5]	Both studies in adults Mean control group % predicted PEF was 36% in 1 study and 64.9% in the other
Clinical severity scores (60 minutes)	The mean dyspnoea VAS was 31.8; the mean Yung ASS was 4.95	SMD 0.01 higher (0.11 lower to 0.12 higher)	-	1130 (2 RCTs)	⊕⊕⊝⊝ LOW [2 6]	1 study reported Yung ASS and the other change in dyspnoea VAS
Admission at first presentation	819 per 1000	778 per 1000 (745 to 819)	RR 0.95 (0.91 to 1.00)	1308 (4 RCTs)	⊕⊕⊕⊝ MODERATE [7 8 9]	Adults vs children test for subgroup difference: P = 0.72, I^2 = 0%
Readmission (7 to 30 days)	26 per 1000	46 per 1000 (22 to 100)	RR 1.80 (0.84 to 3.87)	750 (2 RCTs)	⊕⊕⊝⊝ LOW [10]	Outcome measured at 7 days in 1 study and 30 days in the other.

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Serious adverse events (during admission)	43 per 1000	Not estimable. See comment.	-	557 (2 RCTs)	⊕⊕⊕⊖ MODERATE [11]	Risk difference: −0.03 (95% CI −0.06 to 0.00) Adults vs children test for subgroup difference: P = 0.39, I^2 = 0% Goodacre 2013 also reported participants with 1 or more SAE within 30 days: 35/332 in the $MgSO_4$ group and 28/358 in the placebo group (RD: 0.03; 95% CI −0.02 to 0.07)
Any adverse event (during admission)	144 per 1000	Not estimable. See comment.	-	1197 (2 RCTs)	⊕⊕⊕⊕ HIGH	Risk Difference: 0.01 (95% CI −0.03 to 0.05) Adults vs children test for subgroup difference: P = 0.34, I^2 = 0% Goodacre 2013 also reported participants with 1 or more adverse event within 30 days: 52/332 in the $MgSO_4$ group and 36/358 in the placebo group (OR 1.66, 95% CI 1.05 to 2.62)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ASS: asthma severity score; **CI:** Confidence interval; **RD:** risk difference; **RR:** Risk ratio; **OR:** Odds ratio; **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] One study contributing most of weight at unclear risk of bias in multiple domains (−1 study limitations)
[2] I^2 > 50% (−1 inconsistency)
[3] Studies equal size but one study contributes almost 90% of weight to analysis due to much smaller standard deviations. Result no longer significant if random-effects model applied (−1 imprecision)
[4] Although one study at unclear risk of bias in several domains, the larger study, which contributes vast majority of weight to analysis, if of high methodological quality (no downgrade)
[5] Although confidence interval includes no difference, they are sufficiently tight to effectively rule out an important between-group difference (no downgrade)
[6] Confidence intervals include both harm and benefit of intervention (−1 imprecision)
[7] Although two of the studies at unclear risk of bias in several domains the two large studies contributing nearly 95% of weight in analysis are both of high methodological quality (no downgrade)
[8] Although the I^2 = 52%, the two large studies contributing to this analysis show consistent results (no downgrade)
[9] Confidence intervals include no difference (−1 imprecision)
[10] Confidence intervals include no difference and appreciable harm or benefit of the intervention (−2 imprecision)

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[11] Events rare and confidence intervals include no difference (−1 imprecision)

Summary of findings 2. $MgSO_4$ + SABA compared to SABA in the treatment of acute asthma

$MgSO_4$+ SABA compared to SABA in the treatment of acute asthma

Patient or population: adults and children with acute exacerbation of asthma
Setting: emergency department/inpatient
Intervention: $MgSO_4$ + SABA
Comparison: SABA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with SABA	Risk with MgSO4 + SABA				
Pulmonary function % predicted FEV1 (20 minutes to 2 to 3 h)	The mean pulmonary function % predicted FEV1 was 56.55%	% predicted FEV1 was 3.34% higher (1.58 lower to 8.26 higher)	-	208 (4 RCTs)	⊕⊕⊝⊝ LOW [1 2]	Adults vs children test for subgroup difference: P = 0.35, I^2 = 0% Severe vs moderate asthma exacerbation test for subgroup difference: P = 0.15, I^2 = 51.8% (favouring a greater effect in the more severe subgroup)
Pulmonary function PEF L/min - Adults (20 minutes to 2 to 3 h)	The mean pulmonary function PEF was 233 L/min	PEF was 11.91 L/min higher (4.12 lower to 27.95 higher)	-	155 (3 RCTs)	⊕⊕⊝⊝ LOW [1 2]	
Pulmonary function PEF L/min - Children (60 minutes)	The mean pulmonary function PEF was 143.5	PEF was 11.9 L/min higher (6.86 lower to 30.66 higher)	-	80 (1 RCT)	⊕⊕⊝⊝ LOW [2 3]	
Admission to hospital at initial presentation	202 per 1000	158 per 1000 (105 to 233)	RR 0.78, (0.52 to 1.15)	375 (6 RCTs)	⊕⊕⊝⊝ LOW [1 2]	Adults vs children test for subgroup difference: P = 0.35, I^2 = 0%
Serious adverse events (During ED/hospital admission)	Not estimable	Not estimable. See comment	-	243 (5 RCTs)	⊕⊕⊝⊝ LOW [1 4]	Risk difference: 0.00 (95% CI −0.04 to 0.04) No events reported

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Any adverse events (During ED/hospital admission)	107 per 1000	Not estimable. See comment	-	694 (5 RCTs)	⊕⊕⊝⊝ LOW [1 2]	Risk difference: −0.01 (95% CI −0.05 to 0.03) Adults vs children test for subgroup difference: P = 0.77, I^2 = 0%

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **ED:** emergency department; **FEV1**: forced expiratory volume in 1 second; **OR:** Odds ratio; **PEF**: peak expiratory flow; **RD**: risk difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Several studies were at unclear or high risk of bias in one or more domain (−1 study limitations)
[2] Confidence intervals include both possible harm and benefit of the intervention (−1 imprecision)
[3] Study at unclear risk of bias in several domains (−1 study limitations)
[4] No events reported but less than 250 participants in total. Risk difference confidence intervals include a possible important harm or benefit of the intervention (−1 imprecision)

Summary of findings 3. MgSO4 compared to SABA in the treatment of acute asthma

$MgSO_4$ compared to SABA in the treatment of acute asthma

Patient or population: adults and children with acute exacerbation of asthma
Setting: emergency department/inpatient
Intervention: $MgSO_4$
Comparison: SABA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with SABA	Risk with MgSO4				
Lung function						Reported narratively in text
Clinical severity score - Fischl index	The Fischl index score was 2.1	Fischl index score 0.13 lower	-	93 (3 RCTs)	⊕⊝⊝⊝ VERY LOW [1 2 3]	Time point 120 minutes in 2 studies and unclear in the third study

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(120 minutes)		(0.62 lower to 0.36 higher)				Wide range of control group scores (0.3, 0.76 and 4.81). Scale out of 7 with higher score indicating more severe symptoms. 4.81 reported in study with unclear time point.
Admission to hospital at initial presentation	118 per 1000	62 per 1000 (6 to 625)	RR 0.53 (0.05 to 5.31)	33 (1 RCT)	⊕⊝⊝⊝ VERY LOW [4 5]	
Serious adverse events (During ED/hospital admission)	Not estimable	Not estimable. See comment		53 (2 RCTs)	⊕⊕⊝⊝ LOW [1 6]	Risk difference: 0.00 (95% CI −0.10 to 0.10) No events reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Several studies at unclear or high risk of bias in one or more domains (−1 study limitations)
[2] Confidence intervals include both possible harm and benefit of the intervention (−1 imprecision)
[3] Time-point for measurement unclear in one study (−1 indirectness)
[4] Study at unclear risk of bias in several domains (−1 study limitations)
[5] One small study. Confidence intervals include appreciable harm or benefit of the intervention (−2 imprecision)
[6] Two small studies. No events reported. Risk difference confidence intervals include appreciable harm or benefit of the intervention (−1 for imprecision)

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BACKGROUND

Description of the condition

Asthma is a chronic respiratory disease characterised by reversible airflow obstruction, with periods of relative control and episodes of deterioration referred to as exacerbations. Exacerbations range in severity from mild to life-threatening and can result in visits to healthcare providers and emergency departments, at times necessitating hospital admission. While rare, admissions to the intensive care setting, mechanical ventilation and deaths from severe acute asthma exacerbations do still occur (NRAD 2014): thus the prevention and treatment of exacerbations are important considerations for everyone with asthma. Due to its chronicity, variability, risk of mortality, and cost to the healthcare system, asthma remains the cause of significant personal and social burden.

Description of the intervention

Asthma exacerbations are characterised by acute episodes of bronchoconstriction and airway inflammation. These episodes generally result in increased requirements for inhaled beta$_2$-agonist (β_2-agonist) therapy (Cates 2004). Unfortunately, in acute asthmatic episodes, β_2-agonists may not be enough to relieve bronchospasm and reduce dyspnoea. The evidence-based guideline for the management of asthma developed by the British Thoracic Society (BTS) and the Scottish Intercollegiate Guideline Network (SIGN) offers comprehensive guidance on the acute and chronic management of asthma in children and adults (BTS/SIGN 2016). Although the management of children and adults is broadly similar, differences remain between the management of acute exacerbations of asthma in children (less than 16 years old) and adults (16 years and older) (BTS/SIGN 2016).

For children and adults seen in an emergency department (ED or A&E) with an asthma exacerbation, the BTS/SIGN guideline recommends inhaled or nebulised β_2-agonists, systemic corticosteroids, and oxygen if needed. International guidelines also recommend the use of inhaled ipratropium for all adults, and children over the age of 5 with severe exacerbations (GINA 2017). For poorly responsive children the next step is nebulised ipratropium (if not already given), and consideration of nebulised magnesium sulfate ($MgSO_4$) if life-threatening features are identified. Intravenous (IV) $MgSO_4$ (Shan 2013), salbutamol and aminophylline are considered if response remains poor. For poorly responsive adults, or those with a life-threatening exacerbation, the addition of nebulised ipratropium (if not already given) is recommended, with consideration of IV $MgSO_4$ (Kew 2014). Nebulised magnesium sulfate is not recommended for the treatment of adults with acute asthma (BTS/SIGN 2016).

How the intervention might work

Magnesium sulfate has been proposed as a possible additive treatment in acute asthma, and has been shown to be effective in severe acute asthma when delivered intravenously (Shan 2013; Kew 2014). It may be effective in acute asthma through one or more of a variety of mechanisms. There is evidence that magnesium sulfate may augment the beta receptor response to salbutamol (Turner 2017). Magnesium sulfate has been shown to relax smooth muscle by inhibiting calcium ion influx (Gourgoulianis 2001); it inhibits acetylcholine and histamine release from cholinergic motor nerve terminals and mast cells respectively (Del Castillo 1954; Bois 1962), and promotes synthesis of nitric oxide (Ashutosh 2000) and prostacyclin (Nadler 1987), which stimulate broncho- and vasodilation. Finally, magnesium ions may have an anti-inflammatory role, attenuating neutrophil activation in adults with asthma (Cairns 1996).

Why it is important to do this review

The potential clinical benefits of nebulised $MgSO_4$ have been studied and research publications have produced conflicting results. Subgroup analysis from one large multi-centre RCT suggests a possible role for $MgSO_4$ in the treatment of children with acute severe asthma (Powell 2013), and has led to current guidance to consider nebulised $MgSO_4$ for children presenting with a life-threatening acute asthma attack (BTS/SIGN 2016). However, nebulised $MgSO_4$ has not yet been used widely in the acute care setting.

In the previous version of this Cochrane Review (Powell 2012), sixteen trials involving 896 patients were included. Seven studies compared nebulised $MgSO_4$ with β_2-agonist to β_2-agonist alone, three studies compared nebulised $MgSO_4$ to β_2-agonist alone, and two studies compared nebulised $MgSO_4$ with β_2-agonist and ipratropium to β_2-agonist and ipratropium alone. The review concluded that there was no good evidence that inhaled $MgSO_4$ could be used as a substitute for inhaled β_2-agonists; and when used in addition to standard inhaled treatments there was no clear evidence of improved pulmonary function or reduced hospital admissions. However, individual study results from three trials suggest possible improved pulmonary function in those with severe asthma exacerbations. The review called for further studies focusing on inhaled $MgSO_4$ in addition to the current guideline treatment for acute asthma and including those with more severe exacerbations.

A 2013 systematic review including nine trials of nebulised magnesium sulfate (some of which were excluded from the 2012 Cochrane Review) identified benefits in pulmonary function for adults treated with nebulised magnesium sulfate compared to placebo (Shan 2013).

Thus, $MgSO_4$ administration in combination with β_2-agonists may be of benefit with respect to pulmonary function in patients presenting to the emergency department with severe acute exacerbations of asthma, and there may be evidence that $MgSO_4$ administered in combination with β_2-agonists reduces hospitalisations. Due to significant heterogeneity among studies, both in terms of treatments and outcome measures, there remains a need for further trials before recommendations can be made regarding the use of nebulised magnesium sulfate for acute asthma exacerbations. The rationale for completing this updated systematic review was to examine the influence any further studies would make on these conclusions.

OBJECTIVES

To determine the efficacy and safety of inhaled $MgSO_4$ administered in acute asthma.

Specific aims: to quantify the effects of inhaled $MgSO_4$ I) in addition to combination treatment with inhaled β_2-agonist and ipratropium bromide, ii) in addition to inhaled β_2-agonist and iii) in comparison to inhaled β_2-agonist.

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METHODS

Criteria for considering studies for this review

Types of studies

We included randomised (or quasi-randomised) controlled trials. We included only parallel study designs; cross-over trials were excluded.

Types of participants

We included studies restricting enrolment to patients with acute asthma; patients with chronic or 'stable' asthma were excluded from the review. We included studies involving all ages; however, we sub-grouped data into adults and children where possible. We accepted any reasonable diagnosis of asthma, namely clinical and guideline-based criteria.

Types of interventions

We included studies where participants were randomised to receive inhaled $MgSO_4$ compared with a control inhaled treatment. That is, studies comparing the efficacy of:

- inhaled $MgSO_4$ and β_2-agonist and ipratropium versus β_2-agonist and ipratropium and placebo;
- inhaled $MgSO_4$ and β_2-agonist versus β_2-agonist and placebo;
- inhaled $MgSO_4$ versus β_2-agonist.

We allowed co-interventions, and recorded information we received about them.

Types of outcome measures

Primary outcomes

Change in pulmonary function from baseline using the following indices.

1. Forced expiratory volume in one second (FEV1) and percentage predicted FEV1;
2. Peak expiratory flow (PEF) and percentage predicted PEF.

Secondary outcomes

1. Clinical severity scores.
2. Proportion of patients requiring admission to hospital.
3. Duration of symptoms.
4. Vital signs (pulse and respiratory rates; systolic and diastolic blood pressure).
5. Adverse events (tremor, nausea, etc).

For the 2017 update, we chose to extract and present outcomes including lung function, vital signs and severity scores at — or as close as possible to — 60 minutes post-baseline. The rationale for this decision is given in the Potential biases in the review process section.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org).
2. Weekly searches of MEDLINE Ovid SP 1946 to date.
3. Weekly searches of Embase Ovid SP 1974 to date.
4. Monthly searches of PsycINFO Ovid SP 1967 to date.
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 1937 to date.
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine).
7. Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in Appendix 1. See Appendix 2 for the search terms we used to identify studies for this review.

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (apps.who.int/trialsearch) (Appendix 2). We searched all sources from their inception to the present and we placed no restriction on the language of publication. Search methods used in the previous version of this review are detailed in Appendix 3. The previously published version included searches up to September 2012. The search period for this update is September 2012 to 6 September 2017.

Searching other resources

We examined the reference lists of all selected articles, primary studies and review articles for relevant studies. We contacted primary authors of studies to request information on additional trials (published and unpublished). We contacted clinicians, colleagues, collaborators and trialists to identify potentially relevant studies. Since $MgSO_4$ is not currently commercially delivered, we did not contact any industry sponsor.

Data collection and analysis

Selection of studies

The selection of studies involved two steps. First, to retrieve studies two independent investigators screened by title, abstract, MeSH headings and keywords the initial search of all databases and reference lists to identify all citations of randomised controlled trials (RCTs) or possible RCTs with potential relevance. We obtained the full texts of those selected articles for 'formal inclusion' review. Second, another review author independently decided on trial inclusion using pre-determined eligibility criteria.

Data extraction and management

We extracted data independently using a standardised data collection form. We extracted the following information, if available: characteristics of the study (design, methods of randomisation, withdrawals/dropouts); participants (age, gender); intervention (type, dose, route of administration, timing and duration of therapy, co-interventions); control (agent and dose); outcomes (types of outcome measures measured and reported,

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timing of outcomes, adverse events); and results. We requested unpublished data from the primary authors when necessary. For this update, two review authors (RK and RN) entered data into Review Manager 2014.

Assessment of risk of bias in included studies

We applied the Cochrane 'Risk of bias' tool in this 2017 update (Higgins 2011). Two review authors (RK and RN) independently assessed the risk of bias for all new included studies for the following six items: random sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other types of bias. We recorded the judgement as high, low or unclear risk of bias and added a description from the trial reports. We discussed any disagreements and resolved them by consensus.

Measures of treatment effect

For dichotomous variables, we expressed data as risk ratio (RR) with 95% confidence intervals (CIs) and reported adverse events as risk difference (RD) together with 95% CIs. For the continuous variables 'pulmonary function' and 'clinical severity score', we reported data as mean differences (MD) or standardised mean differences (SMD) with 95% CIs.

Unit of analysis issues

The unit of analysis was the patient.

Dealing with missing data

If baseline or outcome data or information on trial design were missing, we attempted to contact trial authors.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots. We also used the Chi^2 test (where a P value < 0.10 indicates substantial heterogeneity); however, we exercised caution in interpretation due to the low power associated with this test. I^2 was calculated and a guide to interpretation is:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

We planned to test for publication bias using a funnel plot if there was a sufficient number of trials included in a single forest plot (more than 10). It should be noted that an asymmetrical funnel plot can be caused by heterogeneity, outcome reporting bias and small-study effects as well as publication bias.

Data synthesis

We combined data using a fixed-effect model except in cases where we identified substantial heterogeneity, as defined above, where we employed a random-effects model as a sensitivity analysis.

Subgroup analysis and investigation of heterogeneity

A priori subgroup analyses were planned to examine the effect of:

1. age (two to 16 years old (paediatric) and > 16 years old (adult));*
2. severity of asthma as measured by pre-administration spirometric deviation from predicted (baseline FEV1 or PEF < 50% predicted).

*For the 2017 update, if the age range of participants was unclear, we classified the study according to average age of participants.

Sensitivity analysis

We planned to conduct sensitivity analyses to assess the effect of the overall risk of bias of included trials, but there were insufficient trials of varied methodological quality in the meta-analysis for a sensitivity analysis (e.g. either all the studies were of similar methodological quality, or removing a trial in which we had concerns about risk of bias made no difference to the pooled result).

For the 2017 update we performed a post-hoc sensitivity analysis using a random-effects model when we encountered a study with unusually small standard deviations, which was therefore dominating the meta-analysis. Results of such random-effects model meta-analyses should be interpreted with caution as the model is based on the assumption of a normal distribution of the true effect from each study; this is problematic in analyses with few studies.

We also employed a random-effects model as a sensitivity analysis if substantial heterogeneity was detected, as previously described.

'Summary of findings' table

For this update we included a 'Summary of findings' table for each main comparison and assessed the quality of the evidence using the five GRADE domains (study limitations, imprecision, inconsistency, indirectness and publication bias). We decided a priori to include lung function, clinical severity scores, hospital admissions and adverse events. We used GRADEPro software (GRADEpro GDT) to create the 'Summary of findings' tables.

RESULTS

Description of studies

Results of the search

The previous version of the review included 16 trials. For this update, the database search yielded 45 records and we identified six records from additional sources. Fourteen records were excluded on the basis of the title or abstract and we assessed 37 full texts for eligibility. We excluded a further 10 full texts, with reasons, and identified three ongoing studies. We included nine new studies (22 records) in the review, bringing the total number of included studies to 25 (43 records). See Figure 1, Characteristics of excluded studies and Characteristics of ongoing studies for further details. In addition, we moved two studies which had previously been excluded to Studies awaiting classification (Abd 1997; Bustamante 2000); and added one additional study to Studies awaiting classification (ISRCTN61336225)

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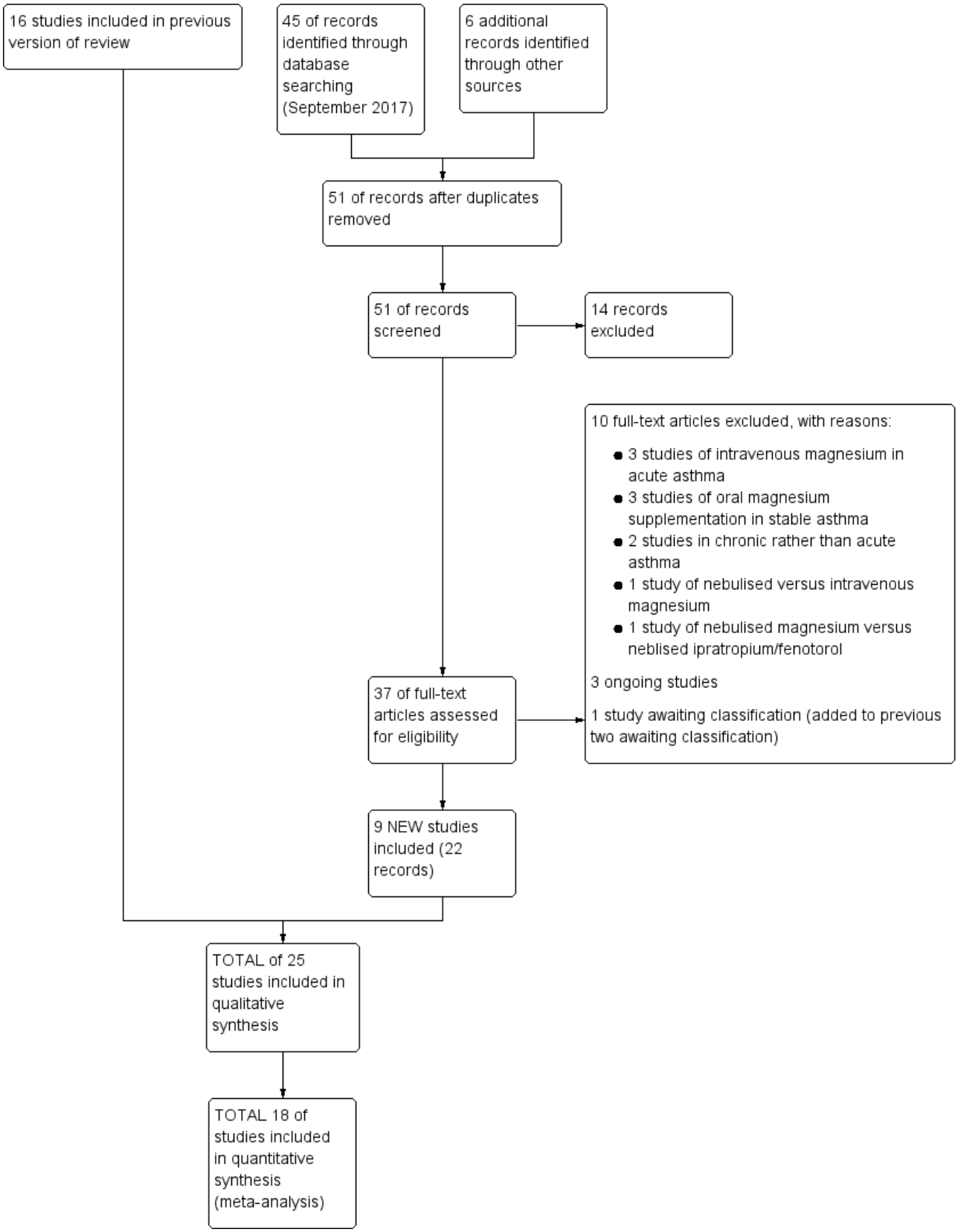
Figure 1. Study flow diagram: review update



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Included studies

We incorporated 25 trials (43 references) including 2907 randomised participants (2777 of whom completed) into the review (see Characteristics of included studies). All of the studies included in this manuscript were published since 1995. There is no particular geographic preference, with Argentina, Egypt, India, Iran, Mexico, New Zealand, Tenerife, Turkey, the UK and the USA represented.

We requested lung function data from the primary authors for two included studies (Meral 1996; Drobina 2006); and further information on trials design and baseline data from four authors (Neki 2006; Badawy 2014; Hossein 2016; Sarhan 2016). We also requested clarification on adverse event data from one author (Powell 2013). With the exception of clarification from the authors of Badawy 2014 and Powell 2013 we did not receive a reply before this review was published. Should information subsequently become available, we will include it in a future update.

Populations

Nine of the 25 included studies involved adults exclusively (Nannini 2000; Abreu-Gonzalez 2002; Bessmertny 2002; Hughes 2003; Kokturk 2005; Gaur 2008; Gallegos-Solórzano 2010; Goodacre 2013; Hossein 2016); and four included adults and children (Mangat 1998; Aggarwal 2006; Neki 2006; Sarhan 2016). Eight studies enrolled children (Meral 1996; Mahajan 2004; Ashtekar 2008; Khashabi 2008; Powell 2013; Mohammedzadeh 2014; Alansari 2015; Turker 2017); and in the remaining four studies the age of participants was not stated (Dadhich 2005; Drobina 2006; Ahmed 2013; Badawy 2014).

The severity of disease varied between studies (Table 1). Fourteen studies enrolled patients based on specific lung function criteria (Meral 1996; Mangat 1998; Nannini 2000; Bessmertny 2002; Hughes 2003; Mahajan 2004; Dadhich 2005; Neki 2006; Gaur 2008; Gallegos-Solórzano 2010; Goodacre 2013; Powell 2013; Alansari 2015; Hossein 2016), while the remaining studies enrolled patients previously diagnosed with asthma using accepted clinical standards, or did not specify how asthma was diagnosed. Based on the baseline demographic data, 15 studies were considered to enrol severe acute exacerbations of asthma (FEV1 or PEF < 50% predicted at baseline or symptom criteria defined by BTS/SIGN guideline) (Meral 1996; Mangat 1998; Nannini 2000; Bessmertny 2002; Hughes 2003; Mahajan 2004; Dadhich 2005; Kokturk 2005; Aggarwal 2006; Neki 2006; Ashtekar 2008; Gaur 2008; Gallegos-Solórzano 2010; Goodacre 2013; Powell 2013).

Sixteen studies recruited participants from emergency departments; two from outpatient or emergency departments (Badawy 2014; Sarhan 2016); and one in a children's assessment unit after general practitioner referral (Ashtekar 2008). Department of presentation was unclear in the remaining six studies (see Table 2).

Badawy 2014 recruited exclusively pregnant women. Due to concerns about baseline imbalance in this study, and the narrow population recruited, we did not include this study in our meta-analyses and instead present the results narratively. The study has been included in another Cochrane Review that addresses asthma treatment options in pregnant women (Bain 2014).

Participants were excluded for a number of reasons including pre-existing lung conditions and features of infection on examination. There was great variation in pharmaceutical exclusion due to drugs taken before recruitment (see Table 2).

Interventions

All studies used nebulised $MgSO_4$ in the intervention group but the comparison and placebo nebulised solutions varied (Table 3). Three studies compared $MgSO_4$ with β_2-agonist directly with no placebo (Meral 1996; Mangat 1998; Neki 2006). Twelve studies compared β_2-agonist with $MgSO_4$ to β_2-agonist with placebo (normal saline) (Nannini 2000; Abreu-Gonzalez 2002; Bessmertny 2002; Hughes 2003; Mahajan 2004; Kokturk 2005; Aggarwal 2006; Khashabi 2008; Ahmed 2013; Badawy 2014; Mohammedzadeh 2014; Turker 2017) . Five studies compared β_2-agonist and ipratropium with $MgSO_4$ to β_2-agonist and ipratropium with placebo (Ashtekar 2008; Gaur 2008; Gallegos-Solórzano 2010; Powell 2013; Hossein 2016), and Drobina 2006 compared β_2-agonist and ipratropium with $MgSO_4$ to β_2-agonist and ipratropium only (i.e. no placebo). Alansari 2015 compared β_2-agonist with $MgSO_4$ to β_2-agonist with placebo (normal saline) after both groups had received one hour of therapy with combined β_2-agonist and ipratropium, and thus is included in comparison one. Two studies had three groups and investigated $MgSO_4$ versus β_2-agonist versus $MgSO_4$ plus β_2-agonist (Dadhich 2005 and Sarhan 2016) and thus appear in comparisons 2 and 3. Goodacre 2013 studied one group with nebulised $MgSO_4$, β_2-agonist, ipratropium and IV placebo, one with IV $MgSO_4$, β_2-agonist, ipratropium and nebulised placebo, and a third group with β_2-agonist, ipratropium and both nebulised and IV placebo. The comparison involving IV $MgSO_4$ has been covered in other reviews (Kew 2014; Griffiths 2016).

Most studies used 0.9% normal saline as placebo; Aggarwal 2006 used distilled water (as well as normal saline) for placebo and Abreu-Gonzalez 2002 used 'physiological serum' as placebo.

We identified the following comparisons which have been used throughout the review to lend structure.

- $MgSO_4$ and β_2-agonist and ipratropium versus placebo (saline) and β_2-agonist and ipratropium (seven studies: Drobina 2006; Ashtekar 2008; Gaur 2008; Gallegos-Solórzano 2010; Goodacre 2013; Powell 2013; Hossein 2016).
- $MgSO_4$ with β_2-agonist versus placebo (saline) and β_2-agonist (15 studies: Nannini 2000; Abreu-Gonzalez 2002; Bessmertny 2002; Hughes 2003; Mahajan 2004; Dadhich 2005; Kokturk 2005; Aggarwal 2006; Khashabi 2008; Ahmed 2013; Badawy 2014; Mohammedzadeh 2014; Alansari 2015; Sarhan 2016; Turker 2017).
- $MgSO_4$ versus β_2-agonist alone (five studies: Meral 1996; Mangat 1998; Dadhich 2005; Neki 2006; Sarhan 2016).

Dose, formulation and dose frequency of $MgSO_4$ differed, meaning that the overall dose of $MgSO_4$ given differed between studies (Table 3). Not all studies reported the concentration of $MgSO_4$ nebulised, but when the information was available most included studies used $MgSO_4$ of similar concentration and osmolality. However, dose per nebulisation and the number of nebulisations performed varied.

Ten studies nebulised three doses of $MgSO_4$ at 20 minutes intervals (Bessmertny 2002; Hughes 2003; Aggarwal 2006; Ashtekar 2008; Gallegos-Solórzano 2010; Goodacre 2013; Powell 2013; Mohammedzadeh 2014; Alansari 2015; Turker 2017). Three studies

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nebulised four doses at 20 minute intervals (Mangat 1998; Neki 2006; Sarhan 2016). Kokturk 2005 nebulised hourly up to four hours after the initial treatment of three doses in one hour. Five studies nebulised only one treatment (Meral 1996; Nannini 2000; Abreu-Gonzalez 2002; Mahajan 2004; Ahmed 2013). Khashabi 2008 gave two doses of treatment but the timing was unclear. Three studies were unclear how frequently the doses were given but probably only one dose was given (Dadhich 2005; Drobina 2006; Gaur 2008). One study gave up to three doses at 20 minute intervals (Badawy 2014). Hossein 2016 gave treatments every 20 to 60 minutes but the total number of doses given was unclear.

All control or placebo interventions were similar in appearance to the treatment drug. The most frequent placebo was saline. One study collected data on participants' ability to distinguish between the treatment and control, and noted no ability to discern (Hughes 2003). Even when not expressly stated, it can reasonably be assumed that the control (placebo) would be similar in appearance to the treatment drug (especially if given in a β_2-agonist vehicle).

Co-interventions

Co-interventions used added complexity and heterogeneity to the review (Table 2). In 11 studies, systemic corticosteroids were administered to all participants, although the timing (before/after nebulised treatment) varied (Mangat 1998; Hughes 2003; Mahajan 2004; Kokturk 2005; Neki 2006; Ashtekar 2008; Gaur 2008; Badawy 2014; Alansari 2015; Sarhan 2016; Turker 2017). In one study, systemic corticosteroids were administered if there was no improvement after the three doses of study treatment (Bessmertny 2002). Overall, 15 studies routinely administered corticosteroids, but in different doses, routes and frequency. In three studies, corticosteroids were administered according to local standard/conventional treatment, or at the clinicians' discretion (Aggarwal 2006; Goodacre 2013; Powell 2013). Meral 1996 gave no further medication as a co-intervention. Six studies made no comments on co-interventions (Nannini 2000; Abreu-Gonzalez 2002; Dadhich 2005; Khashabi 2008; Ahmed 2013; Mohammedzadeh 2014).

Outcomes

A summary of the outcomes relevant to this review reported in the included studies is given in Table 4.

Ongoing trials and unpublished data

We have identified three ongoing studies relevant to this review (Motamed 2015; Saucedo 2015; Schuh 2016a).

Excluded studies

During the history of this review, 65 studies have been excluded for the following reasons: 19 not acute asthma, 12 reviews articles, 11 not randomised controlled trials, eight investigated intravenous magnesium sulfate, seven investigated oral supplements, two investigated intravenous versus inhaled magnesium sulfate, two letters, one study unobtainable, one editorial, one study comparing nebulised magnesium sulfate to ipratropium/fenoterol, and one study in bronchiolitis (see Characteristics of excluded studies).

Risk of bias in included studies

See Figure 2 for summary of the risk of bias judgements.

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Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

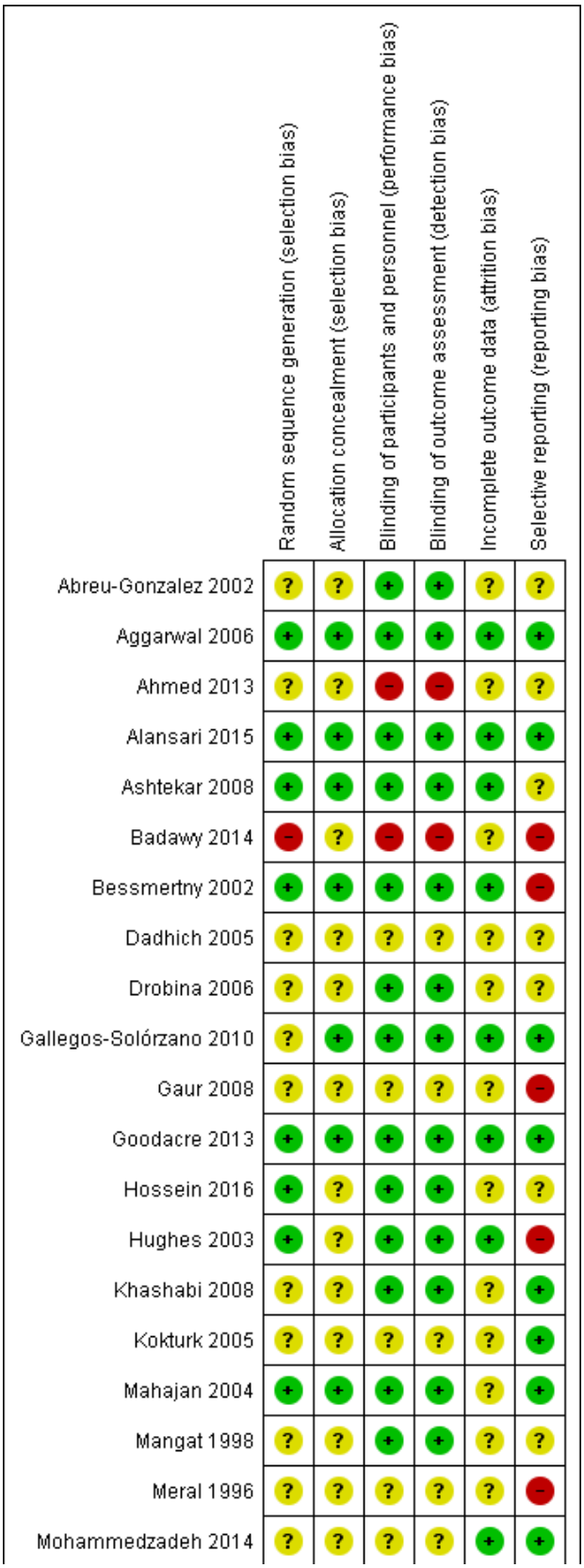

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Figure 2. (Continued)

Allocation

Fourteen studies were described as 'randomised' but the method of sequence generation was not described; these studies were therefore at an unclear risk of bias (Abreu-Gonzalez 2002; Ahmed 2013; Dadhich 2005; Drobina 2006; Gallegos-Solórzano 2010; Gaur 2008; Khashabi 2008; Kokturk 2005; Mangat 1998; Meral 1996; Mohammedzadeh 2014; Nannini 2000; Sarhan 2016; Turker 2017). One further study was at an unclear risk of bias as it is not clear if the study was randomised; we contacted the author for clarification but received no response (Neki 2006). One study was described as 'randomised' but no indication was given of random sequence generation and we were unable to confirm that the groups were balanced with regard to baseline clinical asthma criteria; this study was at high risk of bias (Badawy 2014).

Nine studies were at low risk of bias (Figure 2): the randomisation lists were computer-generated for four studies (Bessmertny 2002; Powell 2013; Alansari 2015; Hossein 2016); produced by the pharmacy for two studies (Hughes 2003; Ashtekar 2008); produced by random number tables for two studies (Mahajan 2004; Aggarwal 2006); and produced by a web-based randomisation system for one study (Goodacre 2013).

No details, or minimal details, were provided on allocation concealment in 17 studies; they were therefore assessed as at unclear risk of bias (Meral 1996; Mangat 1998; Nannini 2000; Abreu-Gonzalez 2002; Hughes 2003; Dadhich 2005; Kokturk 2005; Drobina 2006; Neki 2006; Gaur 2008; Khashabi 2008; Ahmed 2013; Badawy 2014; Mohammedzadeh 2014; Hossein 2016; Sarhan 2016; Turker 2017). A description of allocation concealment was provided in eight studies and they were assessed as at low risk of bias (Bessmertny 2002; Mahajan 2004; Aggarwal 2006; Ashtekar 2008; Gallegos-Solórzano 2010; Goodacre 2013; Powell 2013; Alansari 2015).

Blinding

Fifteen studies gave details as to their double blinding and were therefore at low risk of bias (Mangat 1998; Nannini 2000; Abreu-Gonzalez 2002; Bessmertny 2002; Hughes 2003; Mahajan 2004; Aggarwal 2006; Drobina 2006; Ashtekar 2008; Khashabi 2008; Gallegos-Solórzano 2010; Goodacre 2013; Powell 2013; Alansari 2015; Hossein 2016). Two studies were single blind and therefore at unclear risk of performance and assessment bias (Kokturk 2005; Gaur 2008). One study was described as an open trial and was at high risk of bias (Ahmed 2013). One study gave no baseline clinical asthma data and no details about blinding and was therefore at high risk of detection bias (Badawy 2014). No details were provided of blinding procedure or who was blinded for eight studies so we deemed them to have an unclear risk of bias (Meral 1996; Dadhich 2005; Kokturk 2005; Neki 2006; Gaur 2008; Mohammedzadeh 2014; Sarhan 2016; Turker 2017).

Incomplete outcome data

Fourteen studies were at unclear risk of attrition bias for the following reasons. Six studies were reported as conference abstracts only, with no details provided regarding dropouts (Abreu-Gonzalez 2002; Dadhich 2005; Drobina 2006; Gaur 2008; Khashabi 2008; Ahmed 2013); and no dropout data were given in six studies (Meral 1996; Mangat 1998; Mahajan 2004; Neki 2006; Hossein 2016; Sarhan 2016). In Kokturk 2005 it appears as though there were no dropouts but the published report states that a participant was later excluded because the final diagnosis was COPD and the treatment group is not stated. On further correspondence, Badawy 2014 gave appropriate reasons for exclusions, but details regarding the groups from which participants were excluded were not given.

There was a high risk of bias in one study as three participants were enrolled more than once; only the initial visit was used in the analysis but the treatment group was not stated (Nannini 2000).

There was a low risk of bias in ten studies, with all randomised participants completing in four studies (Aggarwal 2006; Ashtekar 2008; Mohammedzadeh 2014; Turker 2017); and reasons fully described for dropouts in six studies (Bessmertny 2002; Hughes 2003; Gallegos-Solórzano 2010; Goodacre 2013; Powell 2013; Alansari 2015).

Selective reporting

Ten studies were at unclear risk of reporting bias. Six studies were only reported in conference abstracts and therefore the risk of selective reporting bias is unclear (Abreu-Gonzalez 2002; Dadhich 2005; Drobina 2006; Neki 2006; Ashtekar 2008; Ahmed 2013). Hossein 2016 was also at unclear risk of bias as not all primary outcome data were reported, adverse events were recorded only as "no treatment-related complications" and there were clear mistakes in the reporting of vital signs. Sarhan 2016 did not distinguish between primary or secondary outcomes, while Mangat 1998 mentioned but did not report two outcomes.

Seven studies were judged to be at high risk of bias. One study was considered at high risk of bias as outcomes were partially reported and not statistically significant (Gaur 2008). Badawy 2014 was at high risk of bias as no primary outcome was stated. On

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further correspondence, adverse event data but no clinical asthma baseline characteristics were given. Bessmertny 2002 did not present data for outcomes which were described as not statistically significant, and only means were presented for FEV1. We did not identify a prospective trial registration for Turker 2017, adverse events were reported as "no side effect caused by magnesium was observed in any of the patients in the study" and the modified pulmonary index score was reported numerically at 120 minutes only. Hughes 2003, Meral 1996 and Nannini 2000 were also at high risk of bias as the trial report stated there was no difference in blood pressure and heart rate between the groups and no data were reported.

Eight studies were judged to be at low risk of bias. Four studies were at low risk of bias as all outcomes stated in the methods were reported, although no protocols were available (Mahajan 2004; Kokturk 2005; Aggarwal 2006; Gallegos-Solórzano 2010). Pre-registered protocols were available for four studies, in which all planned outcomes were reported (Goodacre 2013; Powell 2013; Mohammedzadeh 2014; Alansari 2015).

Other potential sources of bias

No other risks of bias were identified.

Effects of interventions

See: **Summary of findings for the main comparison** MgSO4 + SABA + ipratropium compared to SABA + ipratropium in the treatment of acute asthma; **Summary of findings 2** $MgSO_4$ + SABA compared to SABA in the treatment of acute asthma; **Summary of findings 3** MgSO4 compared to SABA in the treatment of acute asthma

As detailed in the Methods section, we have presented effects of interventions within the following comparisons.

- $MgSO_4$ and β_2-agonist and ipratropium versus placebo (saline) and β_2-agonist and ipratropium (comparison 1).
- $MgSO_4$ with β_2-agonist versus placebo (saline) and β_2-agonist (comparison 2).
- $MgSO_4$ versus β_2-agonist alone (comparison 3).

$MgSO_4$ and β_2-agonist and ipratropium versus placebo (saline) and β_2-agonist and ipratropium (comparison 1)

Pulmonary function

Four studies including 1279 participants reported on FEV1 or PEF (Gaur 2008; Gallegos-Solórzano 2010; Goodacre 2013; Hossein 2016).

Gallegos-Solórzano 2010 and Gaur 2008, both adult studies, reported a greater %FEV1 in the $MgSO_4$ and β_2-agonist and ipratropium group at 90 minutes (MD: 8.57, 95% CI 1.99 to 15.15; participants = 60) and 120 minutes (MD: 2.60, 95% CI 0.25 to 4.95; participants = 60) respectively with the pooled fixed-effect result favouring the $MgSO_4$ intervention (MD 3.28, 95% CI 1.06 to 5.49; participants = 120; studies = 2; I^2 = 64%; Analysis 1.1).

Despite being similar-sized studies, Gaur 2008 contributed nearly 90% of the weight to the pooled analysis due to reporting much smaller standard deviations. Sensitivity analysis with a random-effects model results in reduced weighting for that study, and increased the size of the CI such that the lower confidence interval included no difference (MD 4.76, 95% CI −0.86 to 10.39; participants = 120; studies = 2).

Hossein 2016 reported a significantly greater per cent predicted PEF in the $MgSO_4$ and β_2-agonist and ipratropium group at 20 minutes (MD 6.90, 95% CI 1.63 to 12.17) but an important between-group difference was not found when 60 minute data were combined with 60 minute data from the large Goodacre 2013 trial (MD 0.05, 95% CI −2.33 to 2.42; participants = 636; studies = 2; I^2 = 67%). A random-effects model substantially increases imprecision, and the effect estimate remains inconclusive. The Goodacre results taken individually did not demonstrate an important between-group difference (MD −0.30%, 95% CI −2.71% to 2.11%).

Alansari 2015, Ashtekar 2008 and Powell 2013 did not report this outcome. Drobina 2006 reported that "peak flow measurements improved over time in both groups ($p < 0.001$). The addition of aerosolized magnesium sulfate did not result in a statistically significant increase in either the maximum or the average peak flow over time ($p = 0.279$ and $p = 0.399$, respectively)." As this research is only available in abstract form, it is unclear how many participants were in each group and no data were reported to include in the meta-analysis.

Clinical severity scores

Powell 2013 reported a lower (therefore better) Yung asthma severity score (ASS) in children receiving $MgSO_4$ and β_2-agonist and ipratropium compared to placebo (saline) and β_2-agonist and ipratropium at 60 minutes (MD −0.23, 95% CI −0.48 to 0.02; participants = 472). The minimal important difference on this nine point scale is not known, but in Powell 2013 it was regarded as 0.5 by the trial steering group. Goodacre 2013 reported no significant difference in the change in dyspnoea visual analogue scale between the groups at 60 (MD 3.10, 95% CI −0.53 to 6.73; participants = 658) or 120 minutes (MD 3.12, 95% CI −1.35 to 7.59; participants = 619). The minimal important difference on the 100 mm scale used in Goodacre 2013 is thought to be 22 mm. When the '60 minute' data from each study are combined using an SMD analysis there is no between-group difference (SMD 0.01, 95% CI −0.11 to 0.12; participants = 1130; studies = 2) but a high level of heterogeneity (I^2 = 83%). As the studies were of a similar size and weight in this analysis, a random-effects model has little impact on the effect estimates, although the confidence interval is widened.

Ashtekar 2008 reported that there was no significant difference between the median area under the curve of ASS of the $MgSO_4$ compared with the placebo-treated group (1530 versus 1355).

Of note: Powell 2013 performed subgroup analysis for asthma severity score, investigating whether participants with a more severe asthma exacerbation or an exacerbation of shorter duration derived more benefit. Although not powered to detect a difference, the study results support the hypothesis that children with more severe exacerbations and children with shorter duration of symptoms prior to presentation benefit more from inhaled $MgSO_4$ as measured using the Yung asthma severity score.

Admission to hospital

Gallegos-Solórzano 2010 reported admissions to the emergency department and the general ward; Goodacre 2013 reported admissions to hospital, HDU and ICU; and Powell 2013 reported admissions to PICU/HDU or intubation.

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Pooled results for adults and children for admissions from the emergency department at initial presentation suggests that admissions are decreased in those receiving $MgSO_4$, β_2-agonist and ipratropium compared to placebo (saline), β_2-agonist and ipratropium (RR 0.95, 95% CI 0.91 to 1.00; participants = 1308; studies = 4; I^2 = 52%) but the upper confidence interval reaches no difference (Analysis 1.4). The overall risk of admission was 82% on placebo which translates into a 78% risk of admission (95% CI 75% to 82%) with nebulised magnesium (Figure 3, Summary of findings for the main comparison). The RR is the same if a random-effects model is used, but the result is less precise (RR 0.95, 95% CI 0.87 to 1.05).

Figure 3. In the control group 82 people out of 100 had hospital admission , compared to 78 (95% CI 75 to 82) out of 100 for the active treatment group.

Gallegos-Solórzano 2010, an adult study, also reported admission to the emergency department (RR 0.38, 95% CI 0.16 to 0.94; participants = 60).

Goodacre 2013 and Gallegos-Solórzano 2010, both adult studies, reported on readmission after initial attendance (up to 7 days in Goodacre 2013; time point unclear in Gallegos-Solórzano 2010). There was no significant difference in admission rates between the two groups, but the result is imprecise (RR 1.80, 95% CI 0.84 to 3.87; participants = 750; studies = 2; I^2 = 37%, Analysis 1.6).

Goodacre 2013 did not detect a between-group difference for either HDU admission (RR 1.19, 95% CI 0.66 to 2.13; participants = 690) or ICU (RR 1.94, 95% CI 0.66 to 5.73; participants = 690) but events were infrequent and both results inconclusive (Analysis 1.5). Similarly Powell 2013, a study in children, reported HDU or ICU admissions/intubations and did not detect a between-group difference (RR 1.48, 95% CI 0.79 to 2.79; participants = 505).

Duration of symptoms

Not reported.

Vital signs

Hossein 2016 and Goodacre 2013 reported on vital signs at various time points. For this update, we chose to present the 60-minute time point in the meta-analysis. There are concerns that administration of $MgSO_4$ may lead to an unwanted drop in blood pressure. Goodacre 2013 reported a significantly higher (therefore better in this context) diastolic blood pressure in participants receiving $MgSO_4$ and β_2-agonist and ipratropium compared to placebo and β_2-agonist and ipratropium at 60 minutes (MD 2.40, 95% CI 0.29 to 4.51; participants = 674), but this difference is unlikely to be clinically meaningful (Analysis 1.10). There was no significant difference in respiratory rate, heart rate or systolic and diastolic blood pressure at any other time point. Similarly there was no

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significant difference in the *change* in vital signs between groups at 60 or 120 minutes (Goodacre 2013; data not shown).

Drobina 2006 stated that vital signs were measured in the conference abstract but data were not reported.

Adverse events

Four studies including 2067 participants reported adverse events (Goodacre 2013; Powell 2013; Alansari 2015; Hossein 2016). During admission, more serious adverse events were reported in the placebo group compared to the $MgSO_4$ group, but only one of the two studies reporting this outcome contributed events and the confidence interval includes no difference (RD −0.03, 95% CI −0.06 to −0.00; participants = 557; studies = 2; I^2 = 0%; Analysis 1.11). There was no significant difference in adverse events between groups for any adverse event (RD 0.01, 95% CI −0.03 to 0.05; participants = 1197; studies = 2; I^2 = 0%; Analysis 1.12).

Goodacre 2013 reported a significantly higher 'all adverse event' rate within 30 days of primary attendance for those participants receiving $MgSO_4$ and β_2-agonist and ipratropium compared to placebo (saline) and β_2-agonist and ipratropium (RD 0.06, 95% CI 0.01 to 0.11; participants = 690; Analysis 1.14) but there was no difference in serious adverse events (Analysis 1.13). Hossein 2016 reported no serious adverse events in either group in the first 60 minutes of treatment.

Both Goodacre 2013 and Powell 2013 reported hypotension and flushing but did not detect a significant between-group difference for either outcome (Analysis 1.15; Analysis 1.16).

Ashtekar 2008 reported that one child had a transiently low blood pressure and another had tingling of the fingers; both received nebulised $MgSO_4$. Drobina 2006 reported that there were no significant side effects noted in either treatment group, but did not report data. Gaur 2008 did not report adverse effects.

Gallegos-Solórzano 2010 reported that the most common adverse reaction associated with $MgSO_4$ was a dry and bitter mouth, but no other side effect was associated with treatment. Electrocardiography (ECG) was abnormal in some participants (43% versus 36%): most commonly, sinus tachycardia (40% versus 36%). One person in the $MgSO_4$ group developed supraventricular extrasystole that did not require additional management. One from each group reported dizziness.

$MgSO_4$ with β_2-agonist versus placebo (saline) and β_2-agonist (comparison 2)

Pulmonary function

Eleven studies involving 589 participants reported at least one measure of lung function (Nannini 2000; Abreu-Gonzalez 2002; Bessmertny 2002; Hughes 2003; Mahajan 2004; Kokturk 2005; Aggarwal 2006; Ahmed 2013; Badawy 2014; Mohammedzadeh 2014; Sarhan 2016).

Five studies reported per cent predicted FEV1; two at 120 minutes (Badawy 2014; Sarhan 2016), two at 60 minutes (Bessmertny 2002; Hughes 2003) and one at 20 minutes (Mahajan 2004). Due to our concerns about potential baseline imbalance and the population recruited in Badawy 2014 (all pregnant women) we chose not to include this study in the analysis.

Pulmonary function based on per cent predicted FEV1 was improved in those who received $MgSO_4$ and a β_2-agonist compared to β_2-agonist and placebo, but the confidence interval includes no difference (MD 3.34, 95% CI −1.58 to 8.26; participants = 208; studies = 4), with moderate between-study heterogeneity identified (I^2 = 43%). We did not detect a difference between adults and children, but only one study involving children contributed to the analysis. We were only able to present subgrouping based on severity at presentation with three studies as we were unable to characterise severity in Sarhan 2016. Results suggest the combination of $MgSO_4$ and salbutamol may be more beneficial in people with a more severe exacerbation (FEV1 < 50% predicted) but the test for subgroup difference was negative (I^2 = 51.8%, P = 0.15). Badawy 2014 reports significantly higher post-treatment per cent predicted FEV1 in pregnant women receiving $MgSO_4$ in addition to salbutamol compared to salbutamol alone; end-point scores were 56.31% (SD 8.25) in the intervention group compared to 32.68% (SD 7.15) (P < 0.001, 30 participants), but baseline FEV1 in each group was not measured.

Six studies reported peak expiratory flow rate (PEF): one at 20 minutes (Nannini 2000), two at 60 minutes (Aggarwal 2006; Mohammedzadeh 2014), two at 120 minutes (Badawy 2014; Sarhan 2016), one at discharge (Kokturk 2005). Where studies reported at more than one time point we have extracted and presented the closest time point to 60 minutes. We excluded Badawy 2014 due to the reasons given above and Kokturk 2005 due to the incompatible time point. We have not pooled adults and children in this analysis. In adults, there was small improvement in PEF compared to the control group, but the confidence interval includes no difference (MD 11.91 L/min, 95% CI −4.12 to 27.95, participants 155, studies 3, I^2 = 13%, Analysis 2.3). A similar small and imprecise effect was seen in Mohammedzadeh 2014, the study involving children: MD 11.90 L/min, 95% CI −6.86 to 30.66, participants 80. Mohammedzadeh 2014 also reports a change from baseline "adjusted % PEF", which favours the combination of $MgSO_4$ and salbutamol compared to salbutamol alone (MD 6.70, 95% CI 3.80 to 9.60; data not displayed). Kokturk 2005 reported "both groups displayed comparable improvement in PEF (%) and clinical scores over 120 min" and displayed results graphically. Discharge mean (SD) per cent predicted PEF was similar in both groups (71.18 (11.55) and 70.50 (12.34)).

One study (Ahmed 2013; an abstract) reported "the percentage increase in peak flow" at 10 and 20 minutes, but the lack of clarity about whether this was a per cent change in the absolute values or a change in the per cent predicted meant we could not include data in the analyses. The study reported a greater improvement in the intervention group compared to the control group at both 10 and 20 minutes (20 (SD 4) vs 13 (3) at 10 minutes; and 35 (7) vs 24 (6) at 20 minutes).

Abreu-Gonzalez 2002 (n = 24), also a conference abstract, selectively reports improvement in PEF at 30 minutes for people in the β_2-agonist and $MgSO_4$ group compared to the placebo plus β_2-agonist group and improvement in FEV1 at 45 minutes for those in the β_2-agonist alone with placebo group compared to the β_2-agonist and $MgSO_4$ group.

Clinical severity score

Four studies involving 575 participants reported clinical severity scores with enough detail for data extraction (Mohammedzadeh

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2014; Alansari 2015; Sarhan 2016; Turker 2017), but we did not perform meta-analysis. Pulmonary index score was significantly lower (therefore better) for those receiving $MgSO_4$ and β_2-agonist compared to β_2-agonist and placebo at 90 minutes in Mohammedzadeh 2014 (MD −0.90, 95% CI −1.43 to −0.37, participants = 80;) but not at other time points. Sarhan 2016 reported no significant difference in change in Fischl index at two hours between the two groups (MD −0.10, 95% CI −1.22 to 1.02; participants = 20; studies = 1). Alansari 2015 reported PRAM asthma severity score at seven time points (from four to 48 hours). PRAM was significantly lower (therefore better) for those receiving placebo (saline) and β_2-agonist and ipratropium compared to $MgSO_4$ and β_2-agonist and ipratropium at the earliest time point (4 hours; MD −0.4, 95% CI −0.7 to −0.01; P = 0.05; participants = 365;) but not at later time points. Turker 2017 measured the modified pulmonary index score at 20, 40 and 120 minutes post baseline but it was only possible to extract data at 120 minutes; no between-group difference was identified (MD 0.38, 95% CI −0.25 to 1.01; participants = 100; studies = 1).

Kokturk 2005 reported that both groups displayed comparable improvement in clinical scores over 120 minutes. Khashabi 2008 reported a non-significant difference in respiratory distress scores, but it is not clear which score was used and the number of participants in each group is not clear. The author was contacted for further information before the 2012 update but no response was received.

Admission to hospital

Six studies involving 375 participants reported admissions for $MgSO_4$ and β_2-agonist compared to β_2-agonist and placebo (Nannini 2000; Hughes 2003; Mahajan 2004; Kokturk 2005; Aggarwal 2006; Turker 2017). Although there was a reduction in the risk of admission for people receiving the $MgSO_4$ intervention, the confidence interval includes no difference (risk ratio 0.78, 95% CI 0.52 to 1.15; participants = 375; studies = 6; I^2 = 0%). It should be noted that this analysis is dominated by evidence from adult studies. As we did not detect any statistical heterogeneity in the analysis we did not perform our prespecified subgroup analyses. One study in children reported that one child from each group required admission/re-admission in the two weeks after discharge (Alansari 2015).

Vital signs

Three studies including 190 participants reported heart rate at 120 minutes (Aggarwal 2006; Badawy 2014; Sarhan 2016). As previously, we have not included Badawy 2014 in the analysis and combining the remaining two studies resulted in such substantial heterogeneity (I^2 = 82%) that we did not perform meta-analysis (Analysis 2.5). Participants receiving $MgSO_4$ and β_2-agonist had a slightly lower (therefore better) heart rate at 120 minutes compared to those receiving β_2-agonist and placebo in Aggarwal 2006 (MD −2.70, 95% CI −6.15 to 0.75; participants = 100), but the opposite effect was seen in Sarhan 2016 (MD 22.60, 95% CI 1.61 to 43.59; participants = 20). Badawy 2014 reported a MD of −25.46 (95% CI −28.38 to −22.54) favouring the $MgSO_4$ group.

There was no significant difference between the two groups in systolic or diastolic blood pressure or respiratory rate in the studies reporting these outcomes.

Adverse events

Serious adverse events were reported by five studies including 243 participants (Nannini 2000; Bessmertny 2002; Hughes 2003; Mahajan 2004; Sarhan 2016). No serious events occurred in any of the studies (Analysis 2.9).

Three studies reported on mild-moderate adverse events (Nannini 2000; Bessmertny 2002; Aggarwal 2006); and two reported all adverse events (Ahmed 2013; Alansari 2015). There was no significant difference in those experiencing one or more events between the two groups (RD −0.01, 95% CI −0.05 to 0.03; participants = 694; studies = 5; I^2 = 0%; Analysis 2.10); and no difference detected between adults and children.

Turker 2017 reports narratively that "no side effect caused by magnesium was observed in any of the patients in the study"; this data has not been included in the forest plots.

Aggarwal 2006 reported that tremor was the same in both groups. Khashabi 2008 reported no side effects but it is not clear how many participants were in each group, so their data were not included in this analysis. Kokturk 2005 reported that two participants in the $MgSO_4$ group and four in the placebo group required additional therapy. Two participants developed transient hypotension after receiving $MgSO_4$ and β_2-agonist. No one needed nebulisation to be withheld. One participant in the placebo group suffered palpitations after the second salbutamol nebulisation. No other side effects were reported. Alansari 2015 reported that no participants experienced hypotension; one participant in the placebo group had excessive cough after the first nebulisation and was withdrawn by his parents; one participant in the $MgSO_4$ group experienced chest tightness and facial rash after the third nebulisation (both resolved after 30 minutes); and one placebo group participant required paediatric ICU admission for refractory status asthmaticus.

$MgSO_4$ versus β_2-agonist alone (comparison 3)

Pulmonary function

Four studies involving 133 participants reported PEF, but due to the range of time points and ways of reporting the outcome we have not presented the results on a forest plot. Mangat 1998 found no significant difference in % predicted PEF for $MgSO_4$ alone compared with β_2-agonist alone at 60 minutes (MD 4.20, 95% CI −12.29 to 20.69; participants = 33). Neki 2006 shows a significant advantage for β_2-agonist alone but the time point reported is unclear (MD −50 L/min, 95% CI −67.83 to −32.17; participants = 4). Meral 1996 reported the mean improvement per group in PEFR (%) at five minutes, favouring the β_2-agonist group (MD −36.77, 95% CI −61.26 to −12.28; participants = 40). Sarhan 2016 reported change in per cent predicted PEF and found no significant difference between groups (MD −1.70, 95% CI −8.45 to 5.05; participants = 20).

Clinical severity score

The Fischl index (a composite of vital signs, PEF and clinical features ranging from 0 to 7 with scores > 4 indicating acute severe asthma) was reported in three studies (Mangat 1998; Neki 2006; Sarhan 2016); and the Davies, Leffert, Drabous score (a composite measure of retraction, nasal flaring, cyanosis and wheeze) in one study (Meral 1996). We pooled the results for studies reporting the Fischl Index, which suggests no significant between-group difference (MD −0.13, 95% CI −0.62 to 0.36; participants = 93; studies = 3; I^2 = 0%).

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Meral 1996 reported the maximum clinical severity score in the first hour (MD −3.20; 95% CI −17.62 to 11.22; participants = 40).

Admission to hospital

There was no significant difference in risk of admission between those receiving $MgSO_4$ alone compared with β_2-agonist alone (RR 0.53, 95% CI 0.05 to 5.31; participants = 33, studies = 1; Analysis 3.2); however, the wide confidence interval indicates, due to there being few events in a small trial, that equivalence cannot be claimed. With a single trial contributing data (Mangat 1998), no additional analyses were possible. Three studies did not appear to measure or report this outcome (Meral 1996; Neki 2006; Sarhan 2016).

Vital signs

Sarhan 2016 reported a significantly lower (therefore better) mean heart rate in people receiving β_2-agonist alone compared to $MgSO_4$ alone (MD 21.20, 95% CI 0.17 to 42.23; participants = 20). Respiratory rate was reported as significantly lower (therefore better) in those receiving $MgSO_4$ alone compared to β_2-agonist alone (MD −2.40, 95% CI −3.91 to −0.89; participants = 60; studies = 2; I^2 = 0%)(Neki 2006; Sarhan 2016). There was no significant difference in systolic or diastolic blood pressure between those receiving $MgSO_4$ alone compared with β_2-agonist alone in the one study which reported this (Analysis 3.5; Analysis 3.6).Two studies did not appear to measure or report these outcomes (Meral 1996; Mangat 1998).

Adverse events

Two studies reported that there were no serious adverse events in either arm (participants = 53; studies = 2) (Mangat 1998; Sarhan 2016). One study reported mild to moderate adverse events and no difference was detected between groups (RD −0.17, 95% CI −0.41 to 0.06; participants = 33; Analysis 3.8). Meral 1996 also reported that there were no adverse events in either group. One study did not report adverse events (Neki 2006).

Reporting biases

Too few studies were included in any meta-analysis to produce a funnel plot. However, the impact of publication bias was likely limited through a thorough search strategy.

DISCUSSION

Summary of main results

This systematic review summarises evidence from twenty-four trials including 2807 randomised participants with acute exacerbations of asthma. The most recent update added three new large trials (Goodacre 2013; Powell 2013; Alansari 2015), as well as several small trials. Overall, the results are conflicting with some, generally small, benefits seen of adding $MgSO_4$ to standard therapy for an exacerbation of asthma. The larger and more recent studies typically show a smaller effect than some of the older/smaller studies. Serious adverse events were rare across all four comparisons, suggesting the treatment is generally well tolerated in people experiencing moderate to severe exacerbations of asthma. Differences between studies in the populations, outcomes reported and time points limited the number of meta-analyses performed.

Comparison 1: $MgSO_4$ and β_2-agonist and ipratropium versus placebo and β_2-agonist and ipratropium

We included seven studies in this comparison and were able to extract data on lung function, clinical severity scores, admissions to hospital, vital signs and adverse events. Although some individual studies reported improvement in lung function indices favouring the intervention group, results were inconsistent and may not be clinically relevant overall. The largest study reporting this outcome reported no between-group difference at 60 minutes (Goodacre 2013).

Similarly, clinical severity scores typically did not demonstrate a benefit of the intervention compared to control. Powell 2013, a large study in children, reported a benefit at 60 minutes using the Yung asthma severity score, but the mean difference is unlikely to be clinically important. Admissions to hospital at initial presentation may be reduced by the addition of inhaled magnesium sulfate, but the upper end of the confidence interval includes no difference (RR 0.95, 95% CI 0.91 to 1.00) and it is hard to compare the studies as in Powell 2013 and Goodacre 2013 almost everyone was admitted to hospital, while in the smaller studies a smaller proportion of participants were admitted.

No difference was detected for re-admissions or escalation of care to ITU/HDU, but events were generally rare. Administration of magnesium sulfate has been associated with hypotension and Goodacre 2013 reported a slightly higher diastolic blood pressure in the control group, but the effect size was small (MD 2.40 mmHg, 95% CI 0.29 to 4.51). No other between-group differences were detected in the studies reporting vital signs. Finally, serious adverse events during admission were rare and only one study contributed to this analysis. There was no difference between groups for all adverse events during admission (RD 0.01, 95% CI −0.03 to 0.05). Goodacre 2013 reported a lower risk of all adverse events in the 30 days after admission in the placebo group, but no difference in serious adverse events (around 10% of people experience a serious adverse event and 15% an adverse event).

Comparison 2: $MgSO_4$ with β_2-agonist versus β_2-agonist

We included 15 studies in this comparison and were able to extract data on lung function, clinical severity scores, admissions to hospital, vital signs and adverse events. While some individual studies reported improvement in lung function indices favouring the intervention group, none of the pooled results showed a clinically meaningful benefit as measured by FEV1 or PEFR. Clinical severity scores were reported using a number of different scales and at different time points, but no consistent difference between the two groups was identified. Pooled results for hospital admission favoured the combination of $MgSO_4$ and β_2-agonist, but the confidence interval includes the possibility of admissions increasing in the intervention group (RR 0.78, 95% CI 0.52 to 1.15). Few studies reported vital signs and of those that did, none detected a significant between-group difference, with results often imprecise. There were no serious adverse events reported by any of the included studies and no between-group difference for all adverse events (RD −0.01, 95% CI −0.05 to 0.03).

Comparison 3: $MgSO_4$ versus β_2-agonist alone

We included five studies in this comparison and were able to extract data on lung function, clinical severity scores, admissions to hospital, vital signs and adverse events. As the evidence for

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use of β_2-agonists in acute asthma is well-established this could be considered a historical comparison, no longer in keeping with current clinical practice. Two studies reported a benefit in lung function of β_2-agonist over $MgSO_4$ alone and two studies reported no difference; we did not pool these results. No between-group difference was detected for clinical severity scores (Fischl index) but results are based on only a few small studies, which measured at different time points (MD −0.13, 95% CI −0.62 to 0.36; participants = 93). Admissions to hospital were only reported by one small study and events were rare, leading to an uncertain result. Effects on vital signs were inconsistent; one small study reported lower heart rate in the β_2-agonist group, while pooled results from two studies found a lower respiratory rate in the $MgSO_4$ group. No serious adverse events were reported in any of the studies in this comparison; one small study reported mild to moderate adverse events but the result is imprecise.

Overall completeness and applicability of evidence

Comparisons 1 and 2, in which $MgSO_4$ was combined with other bronchodilators, are the most consistent with current clinical guidance, and therefore most applicable to practice (BTS/SIGN 2016; GINA 2017). Comparison 3, in which $MgSO_4$ was the only inhaled bronchodilator given during the intervention period in one arm, could be considered a more historical comparison. Given the strong evidence of the efficacy of beta-agonists in acute asthma, it is unlikely that studies with this design would receive ethical approval in many settings.

Within comparisons 1 and 2, populations, interventions, outcomes and time points were heterogeneous, which limited the number of meta-analyses performed and therefore the conclusions reached. However three large, well-powered studies of high methodological quality were added to this 2017 update and overall did not demonstrate a substantial benefit of the addition of inhaled $MgSO_4$ to standard therapy (Goodacre 2013; Powell 2013; Alansari 2015), although modest benefits were seen in some individual studies and meta-analyses. However, we were not able to fully implement our planned subgroup analysis for severity and thus there remains uncertainty about whether those with more severe exacerbations derive greater benefit.

The included studies used a variety of different dosing regimens for $MgSO_4$, including different numbers and frequency of doses and different $MgSO_4$ formulations. The precise regimen was not described in all included studies (Table 3). A limitation of this review is that we did not attempt to subgroup studies according to dosing regimen used. It is possible that this is an important effect modifier which may require further investigation. Also, we have not attempted to explore the cost-effectiveness of using inhaled $MgSO_4$; any clinical benefits need to be considered in the context of possible increased costs associated with delivering $MgSO_4$ and monitoring patients during treatment.

We chose lung function (FEV1 and PEFR) as the primary outcome in this review. Lung function may be considered a surrogate outcome in asthma and does not always correlate well with a patient's symptoms, quality of life and asthma control (Carranza Rosenzweig 2004; Aburuz 2005). In an acute setting, however, lung function — particularly peak flow — is frequently used to guide management and assess response to therapy; and validated patient-reported outcomes such as the Asthma Control Questionnaire and Asthma Quality of Life Questionnaire have limited applicability during acute exacerbations.

Other uncertainties in the findings are introduced by the lack of consistency between settings in deciding whether, and if so when, to admit patients from the emergency department into the hospital. There were marked differences between studies in terms of the proportion of patients admitted; this may reflect different practices in different hospitals, varied exacerbation severity in those recruited and differences between practices in paediatric and adult populations. Although these variations should be accounted for in the randomisation process within each trial, it introduces clinical heterogeneity into our meta-analyses and further complicates the interpretation of the evidence.

Finally, adverse events were not consistently reported by all studies. However, we were able to extract data extracted from the more recent larger studies and the combined evidence suggest that inhaled $MgSO_4$ is unlikely to be associated with an important increase in serious adverse events in the populations studied — it should be noted that events were rare.

Quality of the evidence

Our confidence in the results presented in this review ranges from high to very low, but overall most of the evidence was rated as being of low or very low quality. This means the true effect may be substantially different from the estimate of the effect presented. Please see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3 for full details of our GRADE assessments. Our confidence was reduced by a number of different considerations.

Most studies were at unclear or high risk of bias in multiple domains; only four studies were considered to be at low risk of bias in all domains (Aggarwal 2006; Goodacre 2013; Powell 2013; Alansari 2015). Many studies did not clearly report their methods of randomisation or allocation. In some studies it was not clear who was masked to treatment group assignment and we had concerns about attrition bias and selective reporting in multiple studies. We downgraded for study limitations when we were judged that a study about which we had important methodological concerns contributed sufficient weight to analysis to potentially affect the overall estimate.

Imprecision was also a problem in many of the meta-analyses with sample sizes too small and events too few to rule out potential important harm or benefit of the intervention. This was a problem in the lung function, hospitalisation and adverse event analyses. Unexplained statistical heterogeneity was encountered less frequently but this may be a result of us being unable to perform meta-analyses with substantial numbers of studies contributing data. Indirectness was not thought to be a problem in any of the outcomes to which we applied GRADE and we did not have sufficient studies in any one analysis to formally assess publication bias using a funnel plot.

Potential biases in the review process

Publication bias may have influenced the result of this meta-analysis. For example, by missing unpublished negative trials we may be over-estimating the effect of $MgSO_4$ treatment. In order to reduce bias, however, a comprehensive and systematic search of the published and unpublished literature for potentially relevant

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studies was conducted and we have recently updated it. This was followed by our attempts to contact corresponding and first authors. However, we recognise that unpublished data may exist.

We conducted our review in accordance with Cochrane methods and have detailed changes between the protocol and the review in Differences between protocol and review section. One such difference, which may have introduced bias, is the selection of the '60 minute' time point for reporting outcomes. Many studies reported outcome at multiple time points and for consistency we selected the outcome closest to 60 minutes from baseline for meta-analysis. We chose this time point by consensus to maximise the homogeneity of pooled results and because this was identified as a clinically relevant time point for decision making about treatment escalation (i.e. there would be an expectation that most patients are showing a response to treatment with an hour). It is conceivable that choice of a different time point might have led to different conclusions, especially for the lung function and clinical severity score indices, which may be more susceptible to fluctuations over short periods of time.

Agreements and disagreements with other studies or reviews

The conclusions in this updated Cochrane Review are broadly consistent with the previous version of the review (Powell 2012): that there may be some modest benefits associated with addition of magnesium sulfate ($MgSO_4$) to standard therapy for acute asthma. However, the addition of several large and well-conducted studies suggests that there is unlikely to be a substantial additional benefit associated with the addition of inhaled $MgSO_4$. Although we now have more data in children and the effect appears to be similar to that seen in adults, formal subgrouping by age was not always possible due to lack of sufficient data and between-trial heterogeneity.

To our knowledge, no other systematic review has included as many primary studies as the present review and therefore conclusions are not entirely comparable and findings are somewhat conflicting. Overall, systematic reviews published to date have failed to demonstrate a conclusive benefit of inhaled magnesium sulfate in acute asthma and have suggested the role of the intervention remains unclear. For example, a systematic review published in 2006 included six studies, all of which are included in the present review. Despite some evidence of benefit, the authors were unable to reach conclusions due to lack of evidence and stated that the role of inhaled magnesium sulfate remains unclear. Similarly, a 2005 review also included six studies and concluded that nebulised $MgSO_4$ may confer some benefits in terms of pulmonary function and hospital admission, but called for more research (Blitz 2005). These findings are also consistent with the systematic review by Mohammed 2007.

More recently, a 2016 systematic review summarised the literature for both inhaled and intravenous magnesium sulfate in children with acute asthma (Su 2017). The review included four studies of nebulised magnesium sulfate in children, three of which we included and one which we excluded as it was a study of methacholine challenge test in stable asthma. The review concluded there was no impact on hospital admission or lung function. Similarly, a 2012 systematic review in adults included six studies of nebulised $MgSO_4$ (all of which are included in the present review) and concluded that there was insufficient evidence to recommend the use of this intervention (Song 2012). A 2016 review identified 10 relevant trials and concluded "adding nebulized $MgSO_4$ neither improved pulmonary function nor reduced the number of hospital admissions in adult patients with acute asthma" (Ling 2016). Finally, a 2013 review of both intravenous and inhaled magnesium sulfate suggested that there is a benefit for adults in terms of hospital admissions and lung function, but no benefit seen in children (Shan 2013). However, this study included only nine trials of inhaled magnesium sulfate, all of which are included in the present review with the exception of one, because we did not consider it to be an RCT.

Finally, two recent Cochrane Reviews have examined the efficacy and safety of intravenous (IV) $MgSO_4$ in adults and children with acute asthma (Griffiths 2016; Kew 2014). The review in adults included 14 studies, randomising over 2000 participants, and concluded that "a single infusion of 1.2 g or 2 g IV $MgSO_4$ over 15 to 30 minutes reduces hospital admissions and improves lung function in adults with acute asthma who have not responded sufficiently to oxygen, nebulised short-acting beta$_2$-agonists and IV corticosteroids". Limited evidence was found for other measures of benefit and safety (Kew 2014). The evidence in children is more limited with only five studies, involving 182 children, included in the review (Griffiths 2016). The authors conclude that IV $MgSO_4$ may reduce the need for hospital admission in children with moderate to severe asthma exacerbations, but emphasise the small number of trials and participants. Clinicians managing acute asthma and considering the use of a magnesium preparation will need to choose between the inhaled and IV route; at this time, the evidence for IV magnesium may seem more persuasive, in keeping with guidance (BTS/SIGN 2016).

AUTHORS' CONCLUSIONS

Implications for practice

Treatment with nebulised $MgSO_4$ may result in modest additional benefits when added to inhaled β_2-agonists and ipratropium bromide, but our confidence in the evidence is low and there remains substantial uncertainty. The recent large, well-designed trials have generally not demonstrated clinically important benefits. Nebulised $MgSO_4$ does not appear to be associated with an increase in serious adverse events or all adverse events, but serious events were rare and results lacked precision. Those with a more severe exacerbation may experience a greater benefit but as we were unable to implement our planned subgroup analysis for severity this remains an area of uncertainty. Evidence regarding the use of nebulised $MgSO_4$ as an alternative to beta-agonists is sparse and inconclusive. Given the wealth of evidence about the use of beta-agonists in acute asthma it seems unlikely that future trials will address this question directly.

Implications for research

Despite including 25 trials in this review update we were unable to pool data for all outcomes of interest and this has limited the strength of the conclusions reached. An agreement on the core outcomes for studies in acute asthma is needed so that any acute asthma study has the same outcomes measured — physiological, cost and those relevant to patients. This is particularly important in paediatric studies where lung function measurement may be more challenging.

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Placebo-controlled trials in patients not responding to standard maximal treatment, including inhaled β_2-agonists and ipratropium bromide and systemic steroids, may help establish if nebulised $MgSO_4$ has a role in acute asthma, although the accumulating evidence suggests that a substantial benefit may be unlikely. Trials comparing the safety and efficacy of inhaled $MgSO_4$ to intravenous $MgSO_4$, including an economic evaluation, are also of interest.

ACKNOWLEDGEMENTS

The original version of this review in 2000 included the following acknowledgment: "The authors would like to acknowledge the assistance of Toby Lasserson and Liz Arnold of the Cochrane Airways Review Group. We would also like to acknowledge Dr. P Mahajan for providing the data from his in revision paper for inclusion into the review. Finally, the assistance of Dr. Chris Cates (Cochrane Airways Review Group Co-ordinating Editor) was greatly appreciated."

The 2012 update of the review included the following acknowledgement: "The authors responsible for the update of this review would particularly like to acknowledge the excellent support and assistance from Emma Welsh, Liz Stovold, and Emma Jackson of the Cochrane Airways Review group, together with the greatly appreciated guidance from Chris Cates (Cochrane Airways Review Group Co-ordinating Editor). We are grateful to Taixiang Wu, Alieksei Seniukovich and Sharon Kramer for kindly providing a translation of studies of potential relevance to the review. The support provided by librarians Judith Scammel, Jane Appleton and Hilary Garrett at St Georges University London is also greatly appreciated."

The 2017 update authors would like to thank Kerry Dwan and Richard Beasley for their contributions to the previous versions of the review. We would also like to acknowledge Chris Cates, Emma Dennett, Emma Jackson and Liz Stovold (members of the Cochrane Airways editorial team) for their support and advice. We thank Mohamed Badawy for providing additional details about Badawy 2014 and Sepideh Banava and Narges Khanjani for their excellent translations of Mohammedzadeh 2014.

Chris Cates was the Editor for this review and commented critically on the review.

The Background and Methods section of this review are based on a standard template used by Cochrane Airways.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Airways Group. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abreu-Gonzalez 2002

Methods	Randomised, controlled, double blind study, 2 groups. 1 centre in Tenerife.
Participants	24 patients (Intervention 13, Control 11), adults, acute asthma, moderate obstruction.

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Abreu-Gonzalez 2002 *(Continued)*

Interventions	Intervention: 2 mL of $MgSO_4$ (isotonic) dose and 400 mcg of salbutamol (delivery probably by MDI). Control: 2 mL of a physiological serum of an inhaled form, 400 mcg of salbutamol (delivery probably by MDI). Nebuliser: no details.
Outcomes	FEV1 and PEF at 0, 15, 30 45 minutes.
Notes	Funding: Gobierno Autonomo Canarias. Abstract only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details but stated as "randomised".
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details.
Selective reporting (reporting bias)	Unclear risk	Abstract only and not all time points reported.

Aggarwal 2006

Methods	Double blind, randomised controlled trial, parallel. 1 emergency department in India.
Participants	Inclusion criteria: participants aged 13 to 60, BTS definition acute asthma (PEF and clinical features). Exclusion criteria: first episode of wheeze, chronic bronchitis or emphysema, heart failure, angina, renal failure, temperature > 38 °C, ET tube required, no consent, pregnancy, failure to do peak flow. Intervention: 50 randomised. Mean age (years): 46.26 (13.96). Men:women: 27:23. Acute severe: 29.

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Aggarwal 2006 *(Continued)*

	Acute life threatening: 21. Smokers: 9. Baseline PEF: 118.6 (41.3). Duration of attack; days (SD) 4.16 (1.69). Control: 50 randomised. Mean age (years): 41.00 (16.66). Men: women: 33:17. Acute severe: 30. Severe life threatening: 20. Smokers: 5. Baseline PEF: 111.6 (43.3). Duration of attack; days (SD) 4.28 (1.99).
Interventions	Intervention: $MgSO_4$ (1 mL of 500 mg/mL $MgSO_4$) and salbutamol (1 mL of salbutamol) 8 mL distilled water – 295 mOsmol/kg ×3 in an hour. Control: salbutamol 1 mL, 1.5 mL distilled water, 7.5 mL normal saline – 287 mOsmol/kg ×3 in an hour. Treatment over 1 h; 3 nebulisers 20 minutes apart. Follow-up for 20 minutes. Ultrasonic nebuliser.
Outcomes	PEF, heart rate, systolic pressure, diastolic pressure, time in ED, blood gases (O_2 and CO_2— 0 and 120 minutes), magnesium levels (0 and 120 minutes). Time points 0, 15, 60, 75, 120 minutes.
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables.
Allocation concealment (selection bias)	Low risk	Separate envelopes to ensure concealment until inclusion (where they were kept and whether tamper proof — not mentioned).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The 2 researchers were blinded to the treatments so measurements (normal clinical outcomes) remained blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	50 participants both sides at beginning and 50 participants both sides completed the study with full outcome data.

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Aggarwal 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	Follow-up data and longer-term outcome data not collected. No apparent indication of selective reporting.

Ahmed 2013

Methods	Randomised open controlled trial. 1 hospital in Bangladesh.
Participants	Inclusion criteria: severe acute asthma. Exclusion criteria: none stated. 120 randomised. Intervention: 60 randomised. Control: 60 randomised.
Interventions	Intervention: salbutamol with $MgSO_4$. Control: salbutamol with normal saline.
Outcomes	PEF, respiratory rate, pulse rate, systolic, diastolic blood pressure, adverse effects.
Notes	Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details but states randomized.
Allocation concealment (selection bias)	Unclear risk	No details given.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear how many participants completed the trial or if any were excluded from analysis.
Selective reporting (reporting bias)	Unclear risk	Conference abstract. no prospective trial registration identified, no outcome measures pre-specified.

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Alansari 2015

Methods	Double-blind, randomised controlled trial. 1 Paediatric emergency centre, Qatar.
Participants	Inclusion criteria: moderate/severe asthma exacerbation, age 2-14 years, previous diagnosis of asthma. Exclusion criteria: prematurity, critical illness needing ICU admission for IV bronchodilator, NIV or invasive ventilation, transfer to other institution, history of hypersensitivity to $MgSO_4$, history of neuromuscular/cardiac/renal disease, underlying structural lung disease, received systemic steroid/theophylline/ipratropium in prior 72 h, consolidation on chest XR, received IV $MgSO_4$ before randomisation, prior participation in the study, haemodynamic instability. Number randomised: 400. Intervention: 208 randomised. Mean age (years): 5.6 (3.1). Male:female: 133:75. Moderate:severe: 168:40. Mean baseline asthma severity score: 7.6 (1.3). Control: 192 randomised. Mean age (years): 5.8 (3.1). Male:female: 115:77. Moderate:severe: 163:29. Mean baseline asthma severity score: 7.5 (1.3).
Interventions	Intervention: 800 mg $MgSO_4$ (15 mL). Control: 15 mL 0.9% NaCl. Medication divided into 3 doses over 1 h. Jet nebuliser.
Outcomes	Time to medical readiness for discharge, mean asthma severity score (4, 8, 12, 24, 36, 48 h), mean asthma severity score at discharge, need for revisit or readmission (2 weeks). Adverse events: chest tightness and facial rash (1; intervention group). Excessive cough (1; control group). ICU admission (1; control group).
Notes	Funding: Hamad Medical Corporation; Number: 12095/12

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation without blocks.
Allocation concealment (selection bias)	Low risk	Randomisation list provided to pharmacy resulted in preparation of identical-appearing sealed numbered vials.
Blinding of participants and personnel (performance bias)	Low risk	All study personnel were blinded to treatment.

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Alansari 2015 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel were blinded to treatment. The paper was not explicit re. outcome assessors – they were assumed to also have been blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Over 90% completed the trial in both arms. Balanced number were excluded from each arm, with reasons given.
Selective reporting (reporting bias)	Low risk	Prospective trial registration. All listed outcomes are reported.

Ashtekar 2008

Methods	Parallel 1 Children's Assessment Unit, 1 hospital (UHW).
Participants	Inclusion criteria: age range 2 to 16 years, acute severe asthma. Exclusion criteria: chronic lung disease, congenital heart disease, unable to understand English. 17 randomised (8 boys). Intervention: 7 completed. Control: 10 completed.
Interventions	Intervention: 2.5 mL isotonic $MgSO_4$ (3 occasions at 20-minute intervals), salbutamol and ipratropium bromide. Control: 2.5 mL isotonic saline (3 occasions at 20-minute intervals), salbutamol and ipratropium bromide. 3 dosages over 1 h: follow-up for 240 minutes.
Outcomes	Asthma severity scores (ASS), the sum of wheeze, accessory muscle use and heart rate, were computed on 6 occasions over 4 h. The primary endpoint was the area under the curve of the ASS at the 6 time points for each child.
Notes	Funding: local R and D pilot funding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation by pharmacy at source – in ED as sequential vials (code in pharmacy).
Allocation concealment (selection bias)	Low risk	As above – absolute concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial described as double blind: as above.

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Ashtekar 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial described as double blind: as above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data collected for the 17 patients.
Selective reporting (reporting bias)	Unclear risk	Abstract only. Outcomes partially reported.

Badawy 2014

Methods	Randomised controlled trial. Outpatient department and Emergency department from 1 hospital, Egypt.
Participants	Inclusion criteria: pregnancy, acute exacerbation of asthma partially or not completely controlled on routine acute asthma therapy. Exclusion criteria: congestive heart failure, history of angina, renal problems, history suggestive of pulmonary oedema, very severe asthma (altered consciousness, respiratory acidosis, needing intubation, arrest), any associated medical illness e.g. diabetes/hypertension, fever > 38°C, inability to perform PEF. Number randomised: 60. All participants female. Intervention: 30 randomised. Mean age (years): 25.7 (3.8). Control: 30 randomised. Mean age (years): 25.9 (4.0).
Interventions	Intervention: 500 mg (1 mL) $MgSO_4$ with 1 mL salbutamol solution and 8 mL 0.9% NaCl. Control: 1 mL salbutamol solution with 9 mL 0.9% NaCl. Treatments given over 8 minutes; max 3 sets of nebulisation 20 minutes apart.
Outcomes	PEF, FEV1, FVC, FEV1/FVC ratio, FEF 25-75%, arterial blood pCO2, pO2 and pH, oxygen saturations, serum potassium. Recorded at end of therapy – assumed to be 2 h from baseline.
Notes	Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were randomly classified into groups comparable in socio-demographic criteria, but no indication is given of random sequence generation. Baseline clinical characteristics are given, and there is no indication that the groups were balanced with regard to clinical criteria.

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Badawy 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Participants were randomized into 2 groups through sealed opaque envelopes, but no indication is given whether participants or research personnel were aware of group allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized into 2 groups through sealed opaque envelopes, but no mention of procedures to blind personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention of procedures to blind personnel.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	On further correspondence, appropriate exclusion criteria were applied but no indication given whether excluded participants were balanced across groups, and no dropout data were given.
Selective reporting (reporting bias)	High risk	No prospective trial registration identified. Primary outcome on which this trial was powered is not stated. On further correspondence, adverse event data were given but no clinical baseline characteristics are given.

Bessmertny 2002

Methods	Design: parallel randomised controlled trial. Method of randomisation: computer-generated random numbers. Concealment of allocation: yes. Blinding: double-blinded, placebo-controlled. Withdrawals/dropouts: 6 (4 unable to complete spirometry, 2 inappropriate randomisation).
Participants	Location: 1 university hospital in Brooklyn, NY. Participants: 74 patients, presenting to the emergency department with acute asthma exacerbation, PEF between 40% and 80% predicted. Exclusions: smoking history > 10 pack years, known hypersensitivity to albuterol or $MgSO_4$, known chronic obstructive pulmonary disease, known history of renal impairment, known history of cardiac dysrhythmias, congestive heart failure or angina, fever more than 38 °C, receipt of theophylline or anti-cholinergic within 2 h of arrival to ED.
Interventions	Treatment: albuterol 2.5 mg/3 mL nebule followed by 384 mg isotonic $MgSO_4$ every 20 min × 3. Control: albuterol 2.5 mg/3 mL nebule followed by normal saline every 20 min × 3.
Outcomes	Measured FEV1 every 20 minutes for 2 h. Adverse events: no serious adverse events noted.
Notes	Funding: supported by an unrestricted educational grant from Astra Pharmaceutical Company; no Astra Pharmaceutical Company products were used in the study. Mouthpieces for the spirometer were supplied at no charge from Mallinkrodt Nellcor Puritan Bennett. Circulaire nebulizers were supplied by Westmed Inc. at a reduced rate.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An assigned third party randomised participants by means of a computer-generated random table (1:1 randomisation) to either the treatment or control group.

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Bessmertny 2002 *(Continued)*

Allocation concealment (selection bias)	Low risk	An assigned third party randomised participants by means of a computer-generated random table (1:1 randomisation) to either the treatment or control group.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, placebo-controlled. A log of the identification number and specific treatment of each participant was kept and remained closed to the investigators until the completion of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded, placebo-controlled. A log of the identification number and specific treatment of each participant was kept and remained closed to the investigators until the completion of the study. Outcomes were assessed every 20 minutes for 2 h.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts: 3 in each group. Albuterol plus normal saline solution (3 unable to complete spirometry); and albuterol plus magnesium (2 inappropriate randomisation, 1 unable to perform spirometry).
Selective reporting (reporting bias)	High risk	Mean values only given for FEV1, no SDs and the text reports that there were no statistically significant differences in FEV1 between the groups. The text also states "The analysis of continuous safety variables (BP, pulse rate, respiratory rate, oxygen saturation, and serum magnesium concentrations) did not demonstrate any clinically or statistically significant differences between the 2 groups at any point during the study."

Dadhich 2005

Methods	Random allocation into 3 groups parallel study.
Participants	Location: 1 emergency department teaching hospital in India. Acute severe asthma , PEF < 50%. Group A = 24 Group B = 26 Group C = 21
Interventions	Group A: salbutamol; Group B; salbutamol and $MgSO_4$; Group C $MgSO_4$ alone; no details on dose or frequency.
Outcomes	FEV1, FVC, FEV1/FVC, PEF, "Vital parameters"
Notes	2 abstracts only (the same). Funding: not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Dadhich 2005 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomly allocated.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details.
Selective reporting (reporting bias)	Unclear risk	Abstract only and no data reported except there was a significant improvement in groups B and C compared to group A.

Drobina 2006

Methods	Parallel.
Participants	A total of 110 participants.
Interventions	Intervention: received the control treatment with the addition of 150 mg of $MgSO_4$ (0.3 mL of 50% $MgSO_4$ heptahydrate) to each nebulised dose of medication. Control: received nebulised treatments of albuterol sulfate 0.5% (5 mg/mL) combined with 0.5 mg of ipratropium bromide 0.02% inhalation solution (Atrovent).
Outcomes	Vital signs and peak flow measurements were also assessed at the end of each treatment (a maximum of 3 treatments) and just prior to discharge. A 24-hour follow-up call was made to each participant, during which peak flow measurements were again obtained.
Notes	Abstract only. Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no detail.
Allocation concealment (selection bias)	Unclear risk	Described as randomised but no detail.

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Drobina 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blind but no detail.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double blind but no detail.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Very limited information – impossible to judge.
Selective reporting (reporting bias)	Unclear risk	Abstract only. Vital signs are mentioned as being recorded but are not reported.

Gallegos-Solórzano 2010

Methods	RCT, parallel
Participants	Inclusion criteria: adults, >18 years in the emergency dept with asthmatic crisis, FEV1 < 60% predicted. Exclusion criteria: smokers, those with ambulatory use of systemic steroids, with associated co-morbidities (neuropathy, nephropathy, heart disease, liver disease), fever at admission, use of dietary supplements with $MgSO_4$, irreversible airway obstruction (persistent abnormal spirometry), near-fatal asthma, requirement of endotracheal intubation at admission, anatomic abnormalities of the bronchial tree (bronchiectasis, tuberculosis), history of pulmonary or thoracic surgery, hypersensitivity to $MgSO_4$, and pregnancy or breastfeeding. Location: National Institute of Respiratory Diseases, a tertiary care teaching hospital and national referral centre in Mexico City. Date of study: June 2008 to March 2009. Intervention: 60 randomised, 30 completed. Mean age (years): 34.3 (12.4). Men:women: 9:21. Control: 52 randomised, 30 completed. Mean age (years): 40.3 (11.6). Men:women: 9:21.
Interventions	Each nebulisation lasted 20 mins. Intervention: standard nebulisation but diluted with 3 mL (333 mg) of 10% isotonic $MgSO_4$ (Magnefusin PISA, Guadalajara, Mexico; 1 g/10 mL). Also received 125 mg of IV methylprednisolone. Control: 1 IV dose of 125 mg methylprednisolone and nebulisation with 7.5 mg of albuterol and 1.5 mg of ipratropium bromide in 3 divided doses. Standard nebulisation diluted in 3 mL of isotonic saline solution (SS) as placebo.
Outcomes	FEV1 post-BD (absolute in litres and as percentage of predicted), clinical improvement, oxygen saturation, admission to the ED, admission to the asthma ward, hospital readmissions.

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Gallegos-Solórzano 2010 *(Continued)*

	At 30-min post-nebulisation, patients were clinically and functionally re-evaluated. Also evaluated at 30 days.
Notes	Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised.
Allocation concealment (selection bias)	Low risk	After randomisation, diluents were prepared by a physician outside the study who was not responsible for the participants' care and only had control of the pre-filled syringes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind. Both diluents are odourless, tasteless and colourless to the eye and did not differ when transparency was measured.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The physician responsible for the participants' care along with the nurse and respiratory therapist were blinded to the type of treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons given for dropouts in both groups in the CONSORT diagram. It seems as though there are a high percentage of dropouts but the majority are post-randomisation exclusions based on exclusion criteria.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the Methods section are reported. Best judgement with no access to trial protocol.

Gaur 2008

Methods	Parallel RCT.
Participants	Age: 18 to 60 years. Location: emergency department of a tertiary referral centre in India. Acute asthma and FEV1 < 30% predicted. Intervention: 30. Control: 30.
Interventions	Intervention: nebulised similarly using isotonic $MgSO_4$ (3 mL of 3.2 g%) as a vehicle – unsure if this is "Nebulized salbutamol and ipratropium". Control: nebulised salbutamol and ipratropium using isotonic saline as a vehicle thrice at 20-min intervals.
Outcomes	FEV% predicted at 120 minutes, pooled discharge rate proportion of groups attaining PEF > 60% predicted and relief in dyspnoea at 30, 60, 90, 120 min).
Notes	Abstract only.

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Gaur 2008 *(Continued)*

	Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single blind – no further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Single blind – no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.
Selective reporting (reporting bias)	High risk	1 outcome partially reported and not significant. Abstract only.

Goodacre 2013

Methods	Double blind, randomised controlled trial. 34 emergency departments, UK.
Participants	Inclusion criteria: severe (BTS/SIGN quantified) asthma attack, age ≥16 years. Exclusion criteria: life-threatening features, contraindication to $MgSO_4$, participant unable to give verbal/written consent, previous participation in the study; criteria amended to exclude those who had received $MgSO_4$ in the past 24 h. 1109 randomised. Intervention 1 (nebulised $MgSO_4$): 339 randomised. Mean age (years): 36.5 (14.8). Men:women: 107:232. Smokers: 98. Mean predicted PEF (L/min): 430 (118.8). Intervention 2 (intravenous $MgSO_4$): 406 randomised. Mean age (years): 35.6 (13.1). Men:women: 130:279. Smokers: 138.

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Goodacre 2013 *(Continued)*

	Mean predicted PEF (L/min): 431.8 (116.9). Control: 364 randomised. Mean age (years): 36.4 (14.1). Men:women: 112:252. Smokers: 127. Mean predicted PEF (L/min): 435.0 (110.8).
Interventions	Intervention 1: 100 mL 0.9% NaCl IV and 2 mmol $MgSO_4$ in 7.5 mL 0.9% NaCl nebulised. Intervention 2: 8 mmol $MgSO_4$ in 100 mL 0.9% NaCl IV and 7.5 mL 0.9% NaCl nebulised. Control: 100 mL 0.9% NaCl IV and 7.5 mL 0.9% NaCl nebulised. IV infusion given once over 20 mins, nebulisers given 3 times, each over 20 minutes.
Outcomes	Admission (4 h, 7 days); change in participant's assessment of breathlessness via visual analogue scale, change in PEF, heart rate, respiratory rate, BP, oxygen saturations (1, 2 h); adverse events (2 h); mortality, length of hospital stay, admission to HDU or ICU. Adverse events: treatment group 41 adverse events; control group 36 adverse events.
Notes	Funding: UK National Institute for Health Research Health Technology Assessment Programme.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple and blocked randomisation sequences used to allocate participants to numbered treatment packs.
Allocation concealment (selection bias)	Low risk	Allocated treatment pack numbers were only revealed after participant details recorded and the participant irreversibly entered into the trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, hospital staff, and research staff were masked to allocated treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, hospital staff, and research staff were masked to allocated treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Over 95% of randomised participants in each arm were included in primary analysis. All participants clearly accounted for in flow diagram. There was an inevitable 'drop off' in participants available at each time point for many of the secondary outcomes; it is unclear what impact this may have had on the results.
Selective reporting (reporting bias)	Low risk	Prospective trial registration identified. All primary and secondary outcomes listed in the trial register were reported.

Hossein 2016

Methods	Double blind, randomised controlled trial.

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Hossein 2016 *(Continued)*

	2 emergency departments, Iran.
Participants	Inclusion criteria: moderate/severe asthma exacerbation defined by PEFR < 40% to 69% predicted or limiting speech/normal activity, age > 16 years. Exclusion criteria: need for immediate intubation, significant impairment of heart function, kidney or liver disease, fever > 38.3 °C, chronic lung disease, pregnancy, lactation, pneumonia. 50 randomised. Intervention: 25 randomised. Mean age (years): 52.4 (16.9). Men:women: 11:14. Acute moderate: 3. Acute severe: 22. Mean predicted PEF (%): 15.1 (4.7). Control: 25 randomised. Mean age (years): 53.9 (16.2). Men:women: 14:11. Acute moderate: 3. Acute severe: 21 Mean predicted PEF (%): 14.7 (6.4).
Interventions	Intervention: 3 mL $MgSO_4$ solution (260 mmol/L) nebulised. Control: 3 mL 0.9% NaCl nebulised. Nebulised medication given every 20 to 60 minutes.
Outcomes	Predicted PEFR (%), oxygen saturations, respiratory rate, dyspnoea severity index (20, 60 minutes); need for admission, serious side-effect rate (60 minutes). Adverse effects: no "serious side-effects" reported.
Notes	Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation software used.
Allocation concealment (selection bias)	Unclear risk	Data not given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both patients and investigators were blinded to the content of identical treatment vials.

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Hossein 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both patients and investigators were blinded to the content of identical treatment vials.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report does not state that all 25 randomised participants in each arm completed the trial, but as the trial finished at 60 mins is it likely that they did.
Selective reporting (reporting bias)	Unclear risk	Trial registered while recruiting. Pre-specified primary and secondary outcomes are reported; note omission of PEFR/dyspnoea scale reporting at 40 mins and no data given to support report of "no treatment-related complications". Clear mistakes in reporting of vital signs.

Hughes 2003

Methods	Design: parallel randomised controlled trial. Method of randomisation: unknown. Concealment of allocation: yes. Blinding: double-blinded, placebo-controlled. Withdrawals/dropouts: 6 (4 COPD, 2 pneumonia).
Participants	Location: 2 university hospitals in New Zealand. Participants: 52 patients, presenting to the emergency department with acute asthma exacerbation, FEV1 < 50% predicted. Exclusions: known irreversible lung disease, pneumonia, pregnancy, significant renal/cardiac impairment, hypotension (sBP < 100 mmHg), required intubation.
Interventions	Standard of care: salbutamol 2.5 mg nebulised ×1 or more, hydrocortisone 100 mg IV at presentation. Treatment: salbutamol 2.5 mg nebule with 2.5 mL isotonic $MgSO_4$ (250 mmol/L) every 30 min ×3. Control: salbutamol 2.5 mg nebule with 2.5 mL normal saline every 30 min ×3. Participants were unable to distinguish solutions.
Outcomes	Measured at baseline and after each treatment (every 30 min ×3): FEV1, % predicted FEV1, BP, heart rate, O_2 saturation. Requirement for admission at 90 minutes. Adverse events: no serious adverse events noted.
Notes	Funding: the study was funded by a research grant from the University of Otago. The study sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to their treatment groups in accordance with the allocation sequence determined by the hospital pharmacy.
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, placebo-controlled. Participants and investigators were unaware of treatment allocation through provision by the hospital pharmacy of pre-prepared identical unmarked syringes containing the study drug.

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Hughes 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded, placebo-controlled. Participants and investigators were unaware of treatment allocation through provision by the hospital pharmacy of pre-prepared identical unmarked syringes containing the study drug. Outcomes assessed every 30 minutes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 in total. $MgSO_4$ (1 COPD, 1 pneumonia). Saline (3 COPD, 1 pneumonia).
Selective reporting (reporting bias)	High risk	The primary outcome, FEV1, was fully reported but other outcomes were not. "The change in blood pressure and heart rate did not differ between the two groups. No clinically significant adverse events were reported."

Khashabi 2008

Methods	Parallel RCT.
Participants	Location: authors based in Iran. Participants: 40 asthmatic children in total between 2 groups. Mean age: 3.55 years.
Interventions	Intervention: nebulised salbutamol, as a vehicle isotonic $MgSO_4$ mixed with salbutamol. Control: nebulised salbutamol, as a vehicle 2.5 mL of normal saline.
Outcomes	Days of hospital stay, hours of need for oxygen, respiratory distress. Measured 1 h before and 1 h after the second course of treatment.
Notes	Abstract only. Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly enrolled.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind.

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Khashabi 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.
Selective reporting (reporting bias)	Low risk	Outcomes stated as measured, reported. Abstract only.

Kokturk 2005

Methods	Parallel RCT
Participants	Inclusion criteria: moderate to severe asthma attacks, 18 to 60 years. Exclusion criteria: patients with febrile disease, diabetes, congestive heart failure, atherosclerotic heart disease, intractable hypertension, chronic obstructive lung disease, renal and hepatic failure and arrhythmia were excluded from the study. Pregnant and breast-feeding women, patients who had already taken theophylline, antihistaminics, and systemic steroids in the previous 24 h, who had acute or chronic respiratory failure, who had been on long-term oxygen therapy, and a history of allergy to salbutamol and $MgSO_4$ have been excluded as well. Location: emergency department, Turkey. Intervention: 14. Mean age: 46.43 (years) (3.31) range 18 to 3. Men:women: 4:10. Control: 12. Mean age: 37.83 (years) (9.26) range 20 to 52. Men:women: 3:9.
Interventions	Every 20 mins for first hour and every hour for the rest of 4 h. Intervention: isotonic $MgSO_4$ (2.5mL) + salbutamol (2.5 mL). Control: salbutamol (2.5 mL) + saline (2.5 mL).
Outcomes	PEF, clinical scores, discharge rates, admission rates. 20th, 60th, 120th, 180th, 240th minute (180 and 240 not compared as most patients completed study in 2 h).
Notes	Funding: not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised – details of sequence generation not included in trial report.
Allocation concealment (selection bias)	Unclear risk	Information not available in trial report.

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Kokturk 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single blind – no further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Single blind – no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information provided in trial report on discharges from both groups up to 240 minutes.
Selective reporting (reporting bias)	Low risk	No apparent indication of selective reporting.

Mahajan 2004

Methods	Design: parallel randomised controlled trial. Method of randomisation: table of random numbers. Concealment of allocation: not stated. Blinding: double-blinded, placebo-controlled. Withdrawals/dropouts: none described.
Participants	Location: 1 paediatric emergency department in Detroit, Michigan. Participants: 62 patients age 5 to 17, presenting to the emergency department with acute asthma exacerbation, FEV1 between 45% and 75% predicted. Exclusions: Fever (> 39 °C), chronic disease (bronchopulmonary dysplasia, cystic fibrosis), known allergy to albuterol or magnesium, received any of steroids, theophylline or ipratropium bromide in the prior 3 days.
Interventions	Treatment: albuterol 2.5 mg nebule with 2.5 mL isotonic $MgSO_4$ (6.3% solution); 1 dose. Control: albuterol 2.5 mg nebule with 2.5 mL normal saline; 1 dose. Both groups received corticosteroids (2 mg/kg) after inhaled treatment.
Outcomes	Lung function (FEV1 and % predicted FEV1) at baseline, then at 10 and 20 minutes after treatment. Also report vital signs and hospital admission rates. State that none of the patients showed any side effects.
Notes	Funding: this work was funded by an unrestricted grant from the Division of Pediatric Emergency Medicine, Children's Hospital of Michigan, Detroit, Michigan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A table of random numbers was used to provide randomisation and this was performed by a senior research pharmacist at the institution.
Allocation concealment (selection bias)	Low risk	A table of random numbers was used to provide randomisation and this was performed by a senior research pharmacist at the institution.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, placebo controlled. The study medications were provided in identical syringes and both the pharmacy and the investigator were blinded to their contents.

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Mahajan 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded, placebo controlled. The study medications were provided in identical syringes and both the pharmacy and the investigator were blinded to their contents. Outcomes assessed at 10 and 20 minutes after treatment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	None described.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section are reported.

Mangat 1998

Methods	Design: parallel randomised controlled trial. Method of randomisation: unknown. Concealment of allocation: yes. Blinding: double-blind, placebo-controlled. Withdrawals/dropouts: 0.
Participants	Location: emergency department, St John's Medical College Hospital, India. Screened: 63. Participants: 33, 12 to 60 years of age, known or newly diagnosed asthmatics with PEF < 300 L/min. Exclusions: patient enrolled at prior presentation, febrile, lower respiratory tract infection, history or evidence of cardiac/renal/hepatic dysfunction, pregnancy, requirement for ventilatory care, oral/parenteral bronchodilators within previous 6 h, steroids within previous 12 h.
Interventions	Standard of care: hydrocortisone 100 mg IV. Treatment: $MgSO_4$ 3 mL (3.2% solution = 95 mg) nebulised every 20 min ×4. Control: salbutamol 3 mL (2.5 mg) nebulised every 20 min ×4.
Outcomes	Clinical score: Fischl Index, clinical examination. Pulmonary function: PEF. Vitals: respiratory rate, heart rate, BP, pulsus paradoxus. Admission rates, vital signs. Adverse events/side effects: • treatment: 1 case mild transient hypotension with spontaneous resolution. • control group: 1 case mild transient hypotension with spontaneous resolution, 1 case palpitations, 2 cases fine tremors in hand.
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised.
Allocation concealment (selection bias)	Unclear risk	Information not available.

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Mangat 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled. Outcomes assessed at 20 minute intervals.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	None described.
Selective reporting (reporting bias)	Unclear risk	Pulsus paradoxus and BP are mentioned but not reported, but pulsus paradoxus is included as part of the Fischl index.

Meral 1996

Methods	Design: randomised controlled trial. Method of randomisation: unknown. Concealment of allocation: unknown. Blinding: unknown. Withdrawals/dropouts: 0.
Participants	Location: Department of Paediatric Asthma of Ege University Hospital, Turkey. Participants: 40 randomly selected and divided into 2 groups of 20. Mean ages 10.6 and 11 years of age. Previously diagnosed as asthmatic using ATS definitions; PEF decreased by ≥ 25%. Exclusions: medication within 12 h of study, cardiac/renal dysfunction.
Interventions	Treatment: $MgSO_4$ 2 mL (280 mmol/L, 258 mOsm, pH 6.7). Control: salbutamol 2.5 mg in 2.5 mL. Administration: nebulised, inhaled over 10 to 15 minutes.
Outcomes	Evaluations at: 5, 15, 30, 60, 180,240 and 360 minutes. Clinical score: Davis-Leffert-Dabbous respiratory distress score pulmonary function: PEF. Adverse reactions/side effects: none observed.
Notes	Funding: not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were randomly selected for the study and divided into 2 groups.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated.

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Meral 1996 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	None described.
Selective reporting (reporting bias)	High risk	No statistical differences were found between the groups for respiratory rate, heart rate and BP. It is also unclear as to the time point reported as although 5 minutes was prespecified, there were also several other time points specified and only the maximum values were presented.

Mohammedzadeh 2014

Methods	Randomised controlled trial. 1 hospital, Iran.
Participants	Inclusion criteria: moderate to severe asthma (GINA-defined) with acute attack. Exclusion criteria: corticosteroid therapy, steroid/theophylline/ipratropium in past 72 h, chronic lung disease e.g. bronchopulmonary dysplasia/CF, allergy to $MgSO_4$ or salbutamol, not co-operative. 80 randomised. Intervention 1 (nebulised $MgSO_4$): 40 randomised. Mean age (years): 9 (2.2). Male:female: 10:30. Control: 40 randomised. Mean age (years): 8.5 (2.4) Male:female: 17:23.
Interventions	Intervention: 3 mL 7.5% $MgSO_4$, 0.15 mg/kg salbutamol. Control: 3 mL normal saline, 0.15 mg/kg salbutamol. 3 doses at 20 minute intervals.
Outcomes	Pulmonary index, PEFR, adjusted PEFR at 30, 60 and 90 minutes
Notes	Funding: Babol University of Medical Sciences – Research and Technology Institute.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "divided into two groups randomly" but no details given.
Allocation concealment (selection bias)	Unclear risk	Data not given.
Blinding of participants and personnel (performance bias)	Unclear risk	Described as "double-blind" in prospective trial registration but no details given.

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Mohammedzadeh 2014 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as "double-blind" in prospective trial registration but no details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up.
Selective reporting (reporting bias)	Low risk	Prospectively registered; planned outcomes were fully reported.

Nannini 2000

Methods	Design: randomised controlled trial. Method of randomisation: unknown. Concealment of allocation: yes. Blinding: double-blind, placebo-controlled. Solutions were pre-packaged in identical appearing vials. Withdrawals/dropouts: 3 participants were enrolled more than once, only the initial visit was used in the analysis.
Participants	Location: emergency departments in 4 Argentinian hospitals. Participants: 35 patients at least 18 years of age presenting to the emergency department with an acute asthma exacerbation who were able to have PEF measured were enrolled. (% predicted PEF: 38 ± 18 in treatment group, 38 ± 12 in control group). Exclusions: current smokers of ≥ 5 pack years, concurrent medical illness, pregnant, breast feeding, oral or parenteral steroids within the previous 7 days.
Interventions	Standard of care: all patients received supplemental oxygen. If patient condition worsened patient may receive salbutamol 2.5 mg nebulised at discretion of physician. Treatment: 0.5 mL salbutamol (2.5 mg) diluted in 3 mL isotonic $MgSO_4$ (286 mOsm, 7.5% = 225 mg). Control: 0.5 mL salbutamol (2.5 mg) diluted in 3 mL normal saline. Administration: jet nebulised using oxygen at 10 L/min via mouthpiece until dry.
Outcomes	Measurements made at baseline, 10 minutes after treatment and 20 minutes after treatment. Pulmonary functions: primary endpoint : % increase in peak flow = ((change/baseline) × 100). Other: peak flow (best of 3 attempts). Vital signs: respiratory rate, pulse rate, BP. Duration of emergency room care. No adverse events reported in either the experimental or control group.
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised.
Allocation concealment (selection bias)	Unclear risk	Information not available.

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Nannini 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 patients were enrolled more than once, only the initial visit was used in the analysis but treatment group not stated.
Selective reporting (reporting bias)	High risk	There were no significant differences between the groups in changes in BP, heart rate, or respiratory rate at either 10 minutes or 20 minutes.

Neki 2006

Methods	Parallel.
Participants	Inclusion criteria: patients in age group of 15 to 60 years with severe bronchial asthma, as judged by Fischl index having PEF < 300 L/min or FEV in 1st second less than 40% of the predicted value were included in the study. Exclusion criteria: all patients who had received oral inhaler or parenteral bronchodilators in the past 6 h or steroid in the previous 12 h were excluded from the study. Adults and children with severe asthma (15 to 60 years) – 40 participants. 30 female and 10 male but unclear how divided between groups. Intervention: 20 completed. Control: 20 completed.
Interventions	Intervention: given 4 doses of nebulised solution of "3.2G%" $MgSO_4$, 20 minutes apart. Control: received 4 doses of nebulised salbutamol (each dose of 3 mL containing 25 mg), 20 minutes apart.
Outcomes	PEF (L/min), respiratory rate, Fischl index and SaO_2.
Notes	Abstract only. Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of random sequence generation not included in trial report. There is no reference to randomisation in trial report and trial not reported as randomised – seeking clarification from author.

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Neki 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report. There is no reference to randomisation in trial report and trial not reported as randomised – seeking clarification from author.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the trial was not blinded, there is a strong likelihood that outcome assessment was not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information.
Selective reporting (reporting bias)	Unclear risk	Abstract only. No apparent indication of selective reporting.

Powell 2013

Methods	Double blind, randomised controlled trial. 30 emergency departments or children's assessment units, UK.
Participants	Inclusion criteria: severe (BTS/SIGN quantified) asthma exacerbation after conventional treatment, age 2 to 16 years. Exclusion criteria: coexisting respiratory disease, severe renal disease, severe liver disease, known pregnancy, known previous reaction to magnesium, inability to give informed consent, previous randomisation into the trial, life-threatening symptoms, current or previous (in the 3 months preceding screening) involvement with a trial of a medicinal product. 508 randomised. Intervention: 252 randomised. Median age (years): 4 (3 to 7). Male:female: 143:109. Control: 256 randomised. Median age (years): 4 (3 to 7). Male:female: 150:106.
Interventions	Intervention: 2.5 mL $MgSO_4$ (250 mmol/L) nebulised. Control: 2.5 mL isotonic saline nebulised. 3 doses given at roughly 20 minute intervals.
Outcomes	Mean Yung asthma severity score, treatment step-down (60 minutes); length of stay, need for additional intravenous bronchodilator, admission to PICU/HDU or intubation, adverse events (until discharge). Adverse events: treatment group 47, control group 59

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Powell 2013 *(Continued)*

Notes	Funding: National Institute of Health Research Health Technology Assessment Programme.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated blocked randomisation sequence stratified by centre was generated by an independent statistician who had no further involvement in the study.
Allocation concealment (selection bias)	Low risk	Treatment packs were identical in appearance and numbered sequentially for each centre.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants (patients, clinicians, research team, and statisticians) were masked to the treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The statistical analyses were completed with masked data, with treatment groups revealed only after final analyses had been completed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Over 90% randomised participants in each arm were included in the adjusted primary analysis. All participants who withdrew or were excluded are clearly accounted for in the flow diagram.
Selective reporting (reporting bias)	Low risk	Prospectively registered trial. All listed outcomes are reported.

Sarhan 2016

Methods	Double blind, randomised controlled trial. Chest and emergency departments at 1 hospital, Egypt.
Participants	Inclusion criteria: diagnosis of asthma. Exclusion criteria: fever, lower respiratory tract infection, cardiac/renal/hepatic dysfunction, needed NIV/intubation, near-fatal asthma, pregnancy, lactation, failed to use PEF meter, inhaled/oral/intravenous bronchodilator use within past 6 h or steroid use within past 12 h. 30 randomised. Intervention 1 (magnesium): 10 randomised. Mean age (years): 33.5 (17.8). Men:women: 4:6. Mean % of predicted PEF at presentation: 33.9 (9.8). Intervention 2 (salbutamol and placebo) : 10 randomised. Mean age (years): 48.6 (9.9). Men:women: 3:7. Mean % of predicted PEF at presentation: 36.4 (10.5).

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Sarhan 2016 *(Continued)*

	Intervention 3 (salbutamol and magnesium): 10 randomised. Mean age (years): 51.3 (15.8). Men:women: 7:3. Mean % of predicted PEF at presentation: 34.1 (9.4).
Interventions	Intervention 1: 3 mL $MgSO_4$ (3.3% solution) nebulised. Intervention 2: 0.5 mL salbutamol (0.5% solution) in 2.5 mL isotonic saline nebulised. Intervention 3: 0.5 mL salbutamol (0.5% solution) in 2.5 mL $MgSO_4$ (4% solution) nebulised. 4 doses given at 20 minute intervals. Ultrasonic nebuliser.
Outcomes	PEF improvement, respiratory rate, heart rate, blood pressure, oxygen saturations, improvement in Fischl index of clinical severity, adverse event rate (all at "final" time point, assumed to be 2 h). Adverse events: no events "severe enough to warrant withdrawal" reported.
Notes	Funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reports patients were randomised into 3 groups but no details given.
Allocation concealment (selection bias)	Unclear risk	Data not given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "double blind" but no details given about who was blinded or how.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as "double blind" but no details given about who was blinded or how.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report does not specify how many randomised participants completed the trial.
Selective reporting (reporting bias)	Unclear risk	No prospective trial registration identified. Primary and secondary outcomes not defined. No power calculation reported.

Turker 2017

Methods	Double blind, randomised controlled trial. 1 emergency department, Turkey
Participants	Inclusion criteria: children aged 3 to 15 years with asthma admitted to the emergency department due to a moderate asthma exacerbation.

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Turker 2017 *(Continued)*

	Exclusion criteria: any associated chronic diseases such as cystic fibrosi and bronchiectasis. 100 randomised. Intervention: 50 randomised. Mean age, months (SD): 76.06 (27.33). Male:female: 25:25. Median (IQR) modified pulmonary index score at presentation 8 (7-8). Control: 50 randomised. Mean age, months (SD): 74.96 (33.65). Male:female: 29/21. Median (IQR) modified pulmonary index score at presentation 7 (7 to 9).
Interventions	Intervention: nebulised salbutamol (0.15 mg/kg) + 1 mL magnesium sulfate (15%) + 1.5 mL isotonic saline. Control: nebulised salbutamol (0.15 mg/kg) + 1.5 mL isotonic saline. 3 doses given at 20 min intervals.
Outcomes	Primary outcome: Modified Pulmonary Index Score (MPIS); secondary outcomes: hospitalisation rates, symptoms of magnesium imbalance such as nausea, vomiting, abdominal pain, chest pain, headache, fatigue, hypotension and fever.
Notes	Funding: "this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were assigned consecutively to the control or intervention group based on a stratified randomisation procedure" but no further detail about how the randomisation sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Data not given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "double-blind" but no details of who was blinded and the blinding procedure.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as "double-blind" but no details of who was blinded and the blinding procedure.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All patients enrolled in the study completed it".
Selective reporting (reporting bias)	High risk	No trial registration or prospective protocol identified. Adverse events reported as: "no side effect caused by magnesium was observed in any of the patients in the study". Modified pulmonary index score reported numerically at

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Turker 2017 *(Continued)*

	120 minutes only; other time points presented graphically with no measure of variance

ASS: Asthma Severity Score (ASS)
ATS: *American Thoracic Society*
BP: blood pressure
BTS: British Thoracic Society
COPD: Chronic obstructive pulmonary disease
ED: emergency department
FEV1: Forced expiratory volume in 1 second
FVC: Forced vital capacity
h: hour(s)
IV: intravenous
MDI: metered dose inhaler
$MgSO_4$: magnesium sulfate
PEF: Peak Expiratory Flow Rate
R&D: research and development
sBP: systolic blood pressure
SD: standard deviation
SIGN: Scottish Intercollegiate Guidelines Network

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Balter 1989	Review
Bede 2003	Oral supplementation in chronic asthma
Bede 2004	Oral supplementation in chronic asthma
Bede 2008	Oral supplementation in chronic asthma
Bernstein 1995	Study does not assess people with acute asthma
Cairns 1996	Study does not assess people with acute asthma
Castillo Rueda 1991	Letter to the Editor
Chande 1992	Study of stable asthma and methacholine challenge tests
Corbridge 1995	Review
DiGregorio 1999	Not a randomised controlled study
Emelyanov 1997	Study not a randomised trial and in mild-to-moderate persistent asthma rather than acute asthma
Emelyanov 1990	Not a randomised controlled trial
Emelyanov 1996	Exercise induced bronchospasm and challenge test. Not a randomised controlled trial.
Fathi 2014	Oral supplementation in chronic asthma
Fedoseev 1991	Study does not assess people with acute asthma and is not a randomised controlled trial
Gandia 2012	Study of stable asthma and methacholine challenge tests

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Study	Reason for exclusion
Gurkan 1999	Randomised controlled trial of intravenous $MgSO_4$
Harari 1998	Review
Hardin 2001	Review
Harmanci 1996	Stable asthma histamine-induced bronchospasm adults
Hill 1995	Study does not assess people with acute asthma. Dose response study in 20 normal individuals and 19 with chronic asthma.
Hill 1997a	Study does not assess people with acute asthma. Stable asthma histamine challenge tests.
Hill 1997b	Stable adult asthma with histamine challenges
Irazuzta 2014	Randomised controlled trial of intravenous $MgSO_4$
Irazuzta 2016	Randomised controlled trial of intravenous $MgSO_4$
Kenyon 2001	Review
Kreutzer 2001	Review
Manzke 1990	Paediatric exercise-induced bronchospasm. Not a randomised controlled trial.
McFadden 1995	Review
Nannini 1997	Study does not assess people with acute asthma
Nunez-Torres 1995	Not a randomised controlled trial
Pelton 1998	Study does not assess people with acute asthma
Pelton 1999	Review
Petrov 2014	Oral supplementation in uncontrolled and partly controlled atopic asthma
Puente-Maestu 1999	Review
Qureshi 1999	Review
Rodger 2003	Oral supplementation on people with unstable asthma
Rodrigo 2000	Systematic review, includes intravenous $MgSO_4$
Rolla 1987a	Study does not assess people with acute asthma
Rolla 1987b	Study does not assess people with acute asthma
Rolla 1988a	Study does not assess people with acute asthma
Rolla 1988b	Letter to the editor
Scarfone 1998	Randomised controlled trial of intravenous $MgSO_4$

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Study	Reason for exclusion
Scarfone 2000	Intravenous $MgSO_4$
Shishimorov 2015	Oral supplementation in children with uncontrolled asthma
Singh 2008a	Intravenous $MgSO_4$
Singh 2008b	Comparison between inhaled versus intravenous $MgSO_4$
Singhi 2014	Randomised controlled trial of intravenous $MgSO_4$
Sinitsina 1991	Not a randomised controlled trial
Skobeloff 1982	Editorial
Sun 2014	Study of stable asthma and methacholine challenge tests
Talukdar 2005	Not a randomised controlled trial
Teeter 1999	Review
Telia 2005	Study does not assess people with acute asthma
Tereshchenko 2006	Looking at ipratropium bromide mixed with either $MgSO_4$ or saline for bronchiolitis (up to age 11.5 months)
Tetikkurt 1992	Study does not assess people with acute asthma
Tetikkurt 1993	Study does not assess people with acute asthma
Torres 2012	Randomised controlled trial of intravenous $MgSO_4$
Watanatham 2015	Randomised controlled trial of intravenous versus nebulised $MgSO_4$
Wijetunge 2002	No response to attempts made to contact first author from 2002 to 2012. First author sadly died in 2014.
Wongwaree 2017	Randomised controlled trial of nebulized magnesium sulfate versus ipratropium bromide/fenoterol in children with severe asthma exacerbation
Xu 2002	Not a randomised controlled trial
Yemelyanov 1997	Study does not assess people with acute asthma
Zandsteeg 2009	Study does not assess people with acute asthma (stable chronic asthma) and is not a randomised controlled trial
Zhu 2003	Intravenous $MgSO_4$ and not a randomised controlled trial

$MgSO_4$: magnesium sulfate

Characteristics of studies awaiting assessment *[ordered by study ID]*

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Abd 1997

Methods	"Ventilatory, cardiovascular and metabolic responses to salbutamol, ipratropium bromide and magnesium sulfate in bronchial asthma: comparative study"
Participants	No details
Interventions	No details
Outcomes	No details
Notes	Full-text unobtainable

Bustamante 2000

Methods	"Inhaled magnesium sulfate as adjunct therapy for moderate to severe asthma exacerbations, a randomized control clinical trial"
Participants	No details
Interventions	No details
Outcomes	No details
Notes	Full-text unobtainable

ISRCTN61336225

Methods	Prospective double-blind placebo controlled trial
Participants	Children diagnosed as asthmatic according to The Global Initiative for Asthma (GINA) guidelines, aged 5 to 14 years old, capable of measuring PEFR, presenting with moderate to severe acute exacerbation according to paediatric asthma severity score and PEFR
Interventions	Group A: participants receive inhaled salbutamol solution (0.15 mL/kg) plus isotonic magnesium sulfate (2 mL) in a nebulizer chamber; Group B: participants receive inhaled salbutamol solution (0.15 mL/kg), diluted with placebo (normal saline 2 mL) in a nebulizer chamber.
Outcomes	1. Asthma severity measured using the Pediatric Asthma Severity Score (PASS) at baseline, 20, 40 and 60 minutes post-nebulisation 2. Oxygen saturation measured using pulse oximetry at baseline, 20, 40 and 60 minutes post-nebulisation 3. Lung function assessed through measuring peak expiratory flow rate (PEFR) at baseline, 20, 40 and 60 minutes post-nebulisation
Notes	Trial stated as complete February 2016 but no associated publication identified. Contact person emailed on 7 September 2017 to enquire about status of results/publication. No response received at time of review publication.

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Characteristics of ongoing studies *[ordered by study ID]*

Motamed 2015

Trial name or title	Comparison of clinical and spirometric response between nebulized salbutamol, $MgSO_4$ and nebulized salbutamol alone in acute asthma attack
Methods	Randomized, double-blind controlled trial 1 hospital, Iran
Participants	Inclusion criteria: having a history of asthma, a minimum 18 years and maximum 65 years Exclusion criteria: COPD; kidney disease; CHF; pneumonitis; underlying respiratory disease 146 randomised
Interventions	Intervention: nebulized $MgSO_4$ 1/5 mL (20 g / 100 mL) with salbutamol 2/5 mL Control: normal saline with nebulized salbutamol 2/5 mL
Outcomes	Clinical state, FEV1, PEFR
Starting date	22 March 2014
Contact information	Hasan_motamed@yahoo.com
Notes	

Saucedo 2015

Trial name or title	Nebulized Magnesium Sulfate as an Adjunct to Standard Therapy in Asthma Exacerbation
Methods	Randomized, double-blind controlled trial 1 paediatric emergency department, Mexico
Participants	Inclusion criteria: clinical history of asthma, clinical diagnosis of moderate or severe asthma exacerbations, age 2 to 15 years Exclusion criteria: coexistence of lung disease, severe kidney or liver disease, pregnancy, previous reaction to magnesium, no parental consent, prior inclusion in this study, presence of life-threatening co-morbidities, need for advanced airway management, life-threatening symptoms. Estimated enrolment: 152
Interventions	Intervention: nebulized salbutamol 2.5 mg (2 to 5 years) or 5 mg (≥ 6 years) and ipratropium bromide 250 mcg mixed with 2.5 mL of isotonic $MgSO_4$ (150 mg) per dose every 20 minutes during the first hour, continued with nebulized standard treatment every hour for 4 h, plus IV methylprednisolone or PO prednisolone 2 mg/kg/day for each treatment. Control: nebulized salbutamol 2.5 mg (2-5 years) or 5 mg (≥ 6 years) and ipratropium bromide 250 mcg mixed with 2.5 mL of isotonic saline per dose every 20 minutes during the first hour, continued with nebulized standard treatment every hour for 4 h, plus IV methylprednisolone or PO prednisolone 2 mg/kg/day for each treatment.
Outcomes	Primary outcome measure: change from Baseline Preschool Respiratory Assessment Measure (PRAM) at 20, 40, 60, 120, 180 and 240 minutes after beginning treatment.

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Saucedo 2015 *(Continued)*

	Secondary outcome measures: rate of hospitalisation at 4 h, change from baseline heart rate, respiratory rate and blood pressure at 20, 40, 60, 120, 180 and 240 minutes after beginning treatment.
Starting date	September 2015
Contact information	abisaipec@msn.com
Notes	Estimated study completion date: January 2018

Schuh 2016a

Trial name or title	Magnesium nebulization utilization in management of paediatric asthma (MagNUM PA) trial: study protocol for a randomized controlled trial
Methods	Randomized double-blind controlled trial in 7 Canadian paediatric emergency departments
Participants	The trial will include 816 otherwise healthy children who are 2 to 17 years old, having had at least 1 previous wheezing episode, have received systemic corticosteroids, and have a Pediatric Respiratory Assessment Measure (PRAM) ≥ 5 points after 3 salbutamol and ipratropium treatments for a current acute asthma exacerbation.
Interventions	3 doses nebulized salbutamol with either 600 mg $MgSO_4$ or placebo 20 min apart.
Outcomes	Primary outcome: hospitalisation within 24 h of the start of the experimental therapy for persistent respiratory distress or supplemental oxygen. Secondary outcomes include all-cause hospitalisation within 24 h, PRAM, vital signs, number of bronchodilator treatments by 240 min, association between the difference in the primary outcome between the groups, age, gender, baseline PRAM, atopy, and “viral induced wheeze” phenotype.
Starting date	November 2014
Contact information	Suzanne Schuh: Suzanne.schuh@sickkids.ca Division of Paediatric Emergency Medicine, The Hospital for Sick Children, Child Health Evaluative Sciences, SickKids Research Institute, University of Toronto, 555 University Avenue, Toronto, ON M5G 1X8, Canada
Notes	Estimated completed: December 2017

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pulmonary function (% FEV1)	2	120	Mean Difference (IV, Fixed, 95% CI)	3.28 [1.06, 5.49]
1.1 90 minutes	1	60	Mean Difference (IV, Fixed, 95% CI)	8.57 [1.99, 15.15]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 120 minutes	1	60	Mean Difference (IV, Fixed, 95% CI)	2.60 [0.25, 4.95]
2 Pulmonary function % predicted PEF	2	636	Mean Difference (IV, Fixed, 95% CI)	0.05 [-2.33, 2.42]
3 Clinical severity scores (closest to 60 mins)	2	1130	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.11, 0.12]
3.1 Yung ASS at 60 minutes	1	472	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.35, 0.02]
3.2 Change in dyspnoea VAS at 60 minutes	1	658	Std. Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.02, 0.28]
4 Admission at first presentation	4	1308	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.91, 1.00]
4.1 Adults	3	800	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.87, 1.03]
4.2 Children	1	508	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.92, 1.01]
5 HDU/ITU admission	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Admission to HDU (adults)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Admission to ICU (adults)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Admission to PICU/HDU or intubation (children)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Readmission	2	750	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.84, 3.87]
7 Respiratory rate at 60 mins	2	723	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.14, 1.53]
8 Heart rate at 60 mins	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9 Systolic blood pressure at 60 mins	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10 Diastolic blood pressure at 60 mins	1	674	Mean Difference (IV, Fixed, 95% CI)	2.40 [0.29, 4.51]
11 Serious adverse events (during admission)	2	557	Risk Difference (M-H, Fixed, 95% CI)	-0.03 [-0.06, -0.00]
11.1 Adults	1	50	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.07, 0.07]
11.2 Children	1	507	Risk Difference (M-H, Fixed, 95% CI)	-0.04 [-0.06, -0.01]
12 Any adverse event (during admission)	2	1197	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.03, 0.05]

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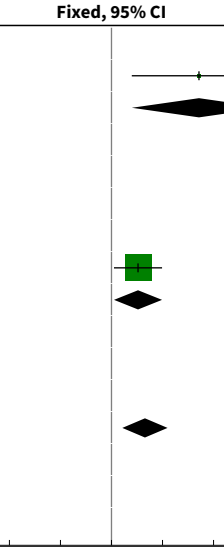
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Adults	1	690	Risk Difference (M-H, Fixed, 95% CI)	0.02 [-0.02, 0.07]
12.2 Children	1	507	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.09, 0.05]
13 Serious adverse events (within 30 days)	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
14 Any adverse event (within 30 days)	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
15 Adverse event: hypotension	2	1197	Risk Difference (M-H, Fixed, 95% CI)	0.02 [-0.01, 0.04]
15.1 Adults	1	690	Risk Difference (M-H, Fixed, 95% CI)	0.03 [-0.01, 0.07]
15.2 Children	1	507	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.02, 0.01]
16 Adverse event: flushing	2	1197	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.01, 0.01]
16.1 Adults	1	690	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.01, 0.02]
16.2 Children	1	507	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.02, 0.01]

Analysis 1.1. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 1 Pulmonary function (% FEV1).

Study or subgroup	MgSO4+SABA+ipra N	MgSO4+SABA+ipra Mean(SD)	Placebo+SABA+ipra N	Placebo+SABA+ipra Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.1.1 90 minutes							
Gallegos-Solórzano 2010	30	69.7 (13.3)	30	61.1 (12.7)		11.35%	8.57[1.99,15.15]
Subtotal ***	**30**		**30**			**11.35%**	**8.57[1.99,15.15]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.55(P=0.01)							
1.1.2 120 minutes							
Gaur 2008	30	60.3 (4.8)	30	57.7 (4.5)		88.65%	2.6[0.25,4.95]
Subtotal ***	**30**		**30**			**88.65%**	**2.6[0.25,4.95]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.16(P=0.03)							
Total ***	**60**		**60**			**100%**	**3.28[1.06,5.49]**
Heterogeneity: Tau^2=0; Chi^2=2.8, df=1(P=0.09); I^2=64.32%							
Test for overall effect: Z=2.9(P=0) Test for subgroup differences: Chi^2=2.8, df=1 (P=0.09), I^2=64.32%							



Favours placebo + SABA + ipratropium

Favours MgSO4 + SABA + ipratropium

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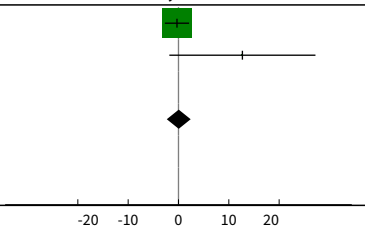
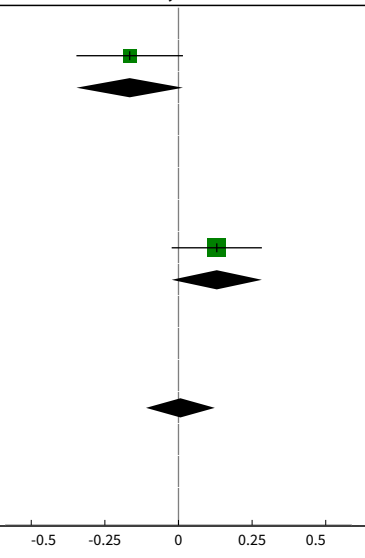
Analysis 1.2. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 2 Pulmonary function % predicted PEF.

Study or subgroup	MgSO4+SABA+ipra N	MgSO4+SABA+ipra Mean(SD)	Placebo+SABA+ipra N	Placebo+SABA+ipra Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goodacre 2013	282	9.9 (15)	304	10.2 (14.7)		97.32%	-0.3[-2.71,2.11]
Hossein 2016	25	48.7 (23.4)	25	36 (28.7)		2.68%	12.7[-1.82,27.22]
Total ***	**307**		**329**			**100%**	**0.05[-2.33,2.42]**
Heterogeneity: Tau²=0; Chi²=3, df=1(P=0.08); I²=66.65%							
Test for overall effect: Z=0.04(P=0.97)							



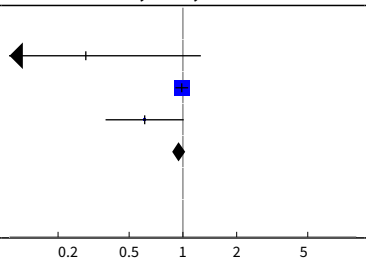
Analysis 1.3. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 3 Clinical severity scores (closest to 60 mins).

Study or subgroup	MgSO4+SABA+ipra N	MgSO4+SABA+ipra Mean(SD)	Placebo+SABA+ipra N	Placebo+SABA+ipra Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.3.1 Yung ASS at 60 minutes							
Powell 2013	228	4.7 (1.4)	244	5 (1.4)		41.76%	-0.17[-0.35,0.02]
Subtotal ***	**228**		**244**			**41.76%**	**-0.17[-0.35,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.8(P=0.07)							
1.3.2 Change in dyspnoea VAS at 60 minutes							
Goodacre 2013	314	-18.4 (22.8)	344	-21.5 (24.7)		58.24%	0.13[-0.02,0.28]
Subtotal ***	**314**		**344**			**58.24%**	**0.13[-0.02,0.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.66(P=0.1)							
Total ***	**542**		**588**			**100%**	**0.01[-0.11,0.12]**
Heterogeneity: Tau²=0; Chi²=5.98, df=1(P=0.01); I²=83.29%							
Test for overall effect: Z=0.11(P=0.91)							
Test for subgroup differences: Chi²=5.98, df=1 (P=0.01), I²=83.29%							



Analysis 1.4. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 4 Admission at first presentation.

Study or subgroup	MgSO4+SA-BA+ipra n/N	Placebo+SA-BA+ipra n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Adults					
Gallegos-Solórzano 2010	2/30	7/30		1.31%	0.29[0.06,1.26]
Goodacre 2013	254/332	278/358		49.95%	0.99[0.91,1.07]
Hossein 2016	11/25	18/25		3.36%	0.61[0.37,1.01]
Subtotal (95% CI)	**387**	**413**		**54.62%**	**0.95[0.87,1.03]**
Total events: 267 (MgSO4+SABA+ipra), 303 (Placebo+SABA+ipra)					
Heterogeneity: Tau²=0; Chi²=6.33, df=2(P=0.04); I²=68.42%					



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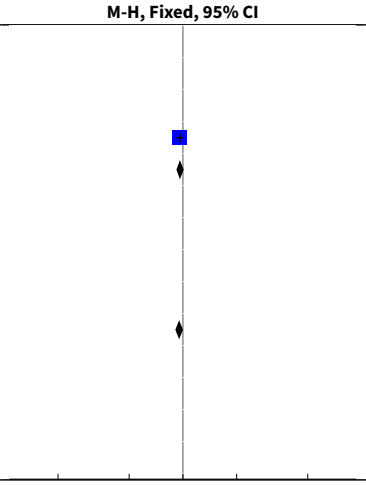
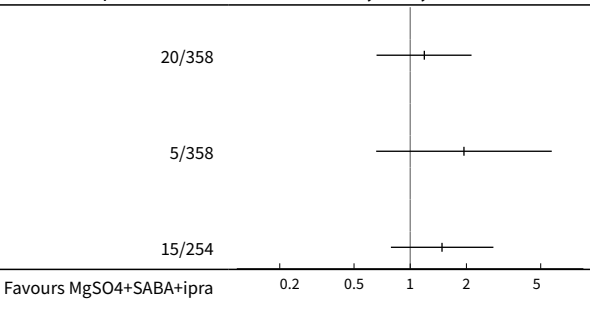
Study or subgroup	MgSO4+SA-BA+ipra n/N	Placebo+SA-BA+ipra n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.33(P=0.18)					
1.4.2 Children					
Powell 2013	232/252	245/256		45.38%	0.96[0.92,1.01]
Subtotal (95% CI)	**252**	**256**		**45.38%**	**0.96[0.92,1.01]**
Total events: 232 (MgSO4+SABA+ipra), 245 (Placebo+SABA+ipra)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.7(P=0.09)					
Total (95% CI)	**639**	**669**		**100%**	**0.95[0.91,1]**
Total events: 499 (MgSO4+SABA+ipra), 548 (Placebo+SABA+ipra)					
Heterogeneity: Tau^2=0; Chi^2=6.3, df=3(P=0.1); I^2=52.39%					
Test for overall effect: Z=1.92(P=0.06)					
Test for subgroup differences: Chi^2=0.13, df=1 (P=0.72), I^2=0%					



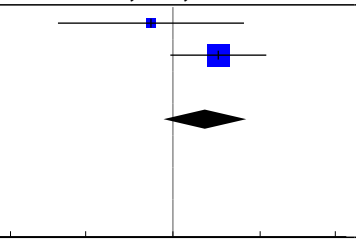
Analysis 1.5. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 5 HDU/ITU admission.

Study or subgroup	MgSO4+SABA+ipra n/N	Placebo+SABA+ipra n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Admission to HDU (adults)				
Goodacre 2013	22/332	20/358		1.19[0.66,2.13]
1.5.2 Admission to ICU (adults)				
Goodacre 2013	9/332	5/358		1.94[0.66,5.73]
1.5.3 Admission to PICU/HDU or intubation (children)				
Powell 2013	22/251	15/254		1.48[0.79,2.79]



Analysis 1.6. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 6 Readmission.

Study or subgroup	MgSO4+SA-BA+ipra n/N	Placebo+SA-BA+ipra n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gallegos-Solórzano 2010	2/30	3/30		30.81%	0.67[0.12,3.71]
Goodacre 2013	15/332	7/358		69.19%	2.31[0.95,5.6]
Total (95% CI)	**362**	**388**		**100%**	**1.8[0.84,3.87]**
Total events: 17 (MgSO4+SABA+ipra), 10 (Placebo+SABA+ipra)					
Heterogeneity: Tau^2=0; Chi^2=1.59, df=1(P=0.21); I^2=37.24%					
Test for overall effect: Z=1.51(P=0.13)					



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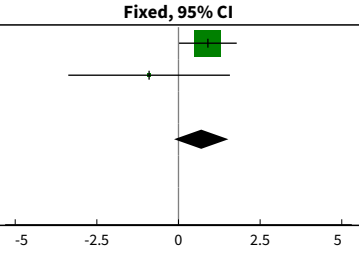
Analysis 1.7. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 7 Respiratory rate at 60 mins.

Study or subgroup	MgSO4+SABA+ipra N	MgSO4+SABA+ipra Mean(SD)	Placebo+SABA+ipra N	Placebo+SABA+ipra Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goodacre 2013	323	22.7 (6.3)	350	21.8 (5.3)		88.7%	0.9[0.02,1.78]
Hossein 2016	25	20.5 (4.8)	25	21.4 (4.1)		11.3%	-0.9[-3.37,1.57]
Total ***	**348**		**375**			**100%**	**0.7[-0.14,1.53]**

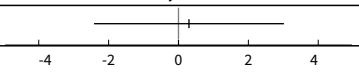
Heterogeneity: Tau^2=0; Chi^2=1.8, df=1(P=0.18); I^2=44.53%

Test for overall effect: Z=1.64(P=0.1)



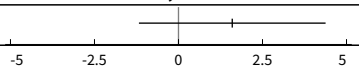
Analysis 1.8. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 8 Heart rate at 60 mins.

Study or subgroup	MgSO4+SABA+ipra N	MgSO4+SABA+ipra Mean(SD)	Placebo+SABA+ipra N	Placebo+SABA+ipra Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goodacre 2013	326	106.8 (18)	353	106.5 (18.1)		0%	0.3[-2.42,3.02]



Analysis 1.9. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 9 Systolic blood pressure at 60 mins.

Study or subgroup	MgSO4+SABA+ipra N	MgSO4+SABA+ipra Mean(SD)	Placebo+SABA+ipra N	Placebo+SABA+ipra Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goodacre 2013	323	128.2 (19.4)	351	126.6 (17.2)		0%	1.6[-1.18,4.38]

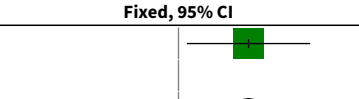


Analysis 1.10. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 10 Diastolic blood pressure at 60 mins.

Study or subgroup	MgSO4+SABA+ipra N	MgSO4+SABA+ipra Mean(SD)	Placebo+SABA+ipra N	Placebo+SABA+ipra Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Goodacre 2013	323	73.2 (14.4)	351	70.8 (13.5)		100%	2.4[0.29,4.51]
Total ***	**323**		**351**			**100%**	**2.4[0.29,4.51]**

Heterogeneity: Not applicable

Test for overall effect: Z=2.23(P=0.03)



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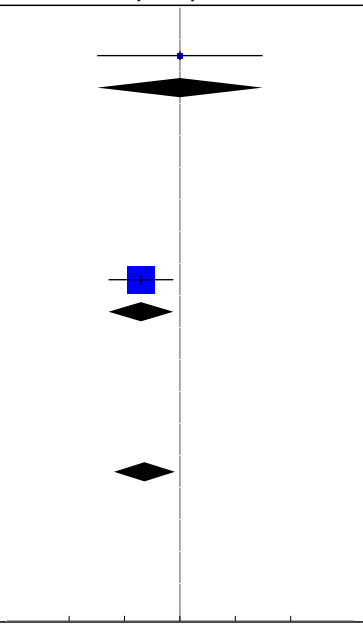
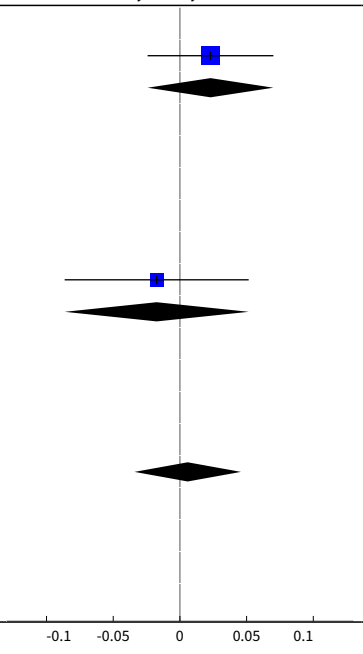
Analysis 1.11. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 11 Serious adverse events (during admission).

Study or subgroup	MgSO4+SABA+ipra n/N	Placebo+SABA+ipra n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
1.11.1 Adults					
Hossein 2016	0/25	0/25		8.98%	0[-0.07,0.07]
Subtotal (95% CI)	**25**	**25**		**8.98%**	**0[-0.07,0.07]**
Total events: 0 (MgSO4+SABA+ipra), 0 (Placebo+SABA+ipra)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.11.2 Children					
Powell 2013	3/252	12/255		91.02%	-0.04[-0.06,-0.01]
Subtotal (95% CI)	**252**	**255**		**91.02%**	**-0.04[-0.06,-0.01]**
Total events: 3 (MgSO4+SABA+ipra), 12 (Placebo+SABA+ipra)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.36(P=0.02)					
Total (95% CI)	**277**	**280**		**100%**	**-0.03[-0.06,-0]**
Total events: 3 (MgSO4+SABA+ipra), 12 (Placebo+SABA+ipra)					
Heterogeneity: Tau²=0; Chi²=0.75, df=1(P=0.39); I²=0%					
Test for overall effect: Z=2.28(P=0.02)					
Test for subgroup differences: Chi²=0.74, df=1 (P=0.39), I²=0%					



Analysis 1.12. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 12 Any adverse event (during admission).

Study or subgroup	MgSO4+SABA+ipra n/N	Placebo+SABA+ipra n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
1.12.1 Adults					
Goodacre 2013	41/332	36/358		57.61%	0.02[-0.02,0.07]
Subtotal (95% CI)	**332**	**358**		**57.61%**	**0.02[-0.02,0.07]**
Total events: 41 (MgSO4+SABA+ipra), 36 (Placebo+SABA+ipra)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.95(P=0.34)					
1.12.2 Children					
Powell 2013	47/252	52/255		42.39%	-0.02[-0.09,0.05]
Subtotal (95% CI)	**252**	**255**		**42.39%**	**-0.02[-0.09,0.05]**
Total events: 47 (MgSO4+SABA+ipra), 52 (Placebo+SABA+ipra)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.62)					
Total (95% CI)	**584**	**613**		**100%**	**0.01[-0.03,0.05]**
Total events: 88 (MgSO4+SABA+ipra), 88 (Placebo+SABA+ipra)					
Heterogeneity: Tau²=0; Chi²=0.94, df=1(P=0.33); I²=0%					
Test for overall effect: Z=0.29(P=0.77)					
Test for subgroup differences: Chi²=0.9, df=1 (P=0.34), I²=0%					



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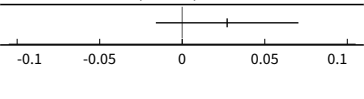
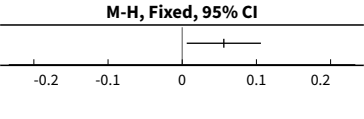
Analysis 1.13. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 13 Serious adverse events (within 30 days).

Study or subgroup	Experimental n/N	Placebo+SABA+ipra n/N	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI
Goodacre 2013	35/332	28/358		0.03[-0.02,0.07]



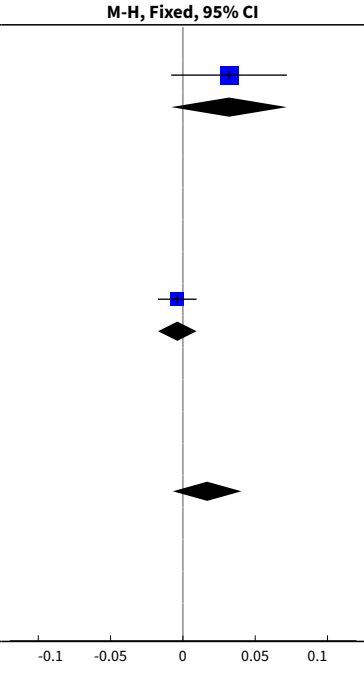
Analysis 1.14. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 14 Any adverse event (within 30 days).

Study or subgroup	Mg+SABA+ipra n/N	Placebo+SABA+ipra n/N	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI
Goodacre 2013	52/332	36/358		0.06[0.01,0.11]



Analysis 1.15. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 15 Adverse event: hypotension.

Study or subgroup	MgSO4+SA-BA+ipra n/N	Placebo+SA-BA+ipra n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
1.15.1 Adults					
Goodacre 2013	31/332	22/358		57.61%	0.03[-0.01,0.07]
Subtotal (95% CI)	**332**	**358**		**57.61%**	**0.03[-0.01,0.07]**
Total events: 31 (MgSO4+SABA+ipra), 22 (Placebo+SABA+ipra)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.56(P=0.12)					
1.15.2 Children					
Powell 2013	1/252	2/255		42.39%	-0[-0.02,0.01]
Subtotal (95% CI)	**252**	**255**		**42.39%**	**-0[-0.02,0.01]**
Total events: 1 (MgSO4+SABA+ipra), 2 (Placebo+SABA+ipra)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
Total (95% CI)	**584**	**613**		**100%**	**0.02[-0.01,0.04]**
Total events: 32 (MgSO4+SABA+ipra), 24 (Placebo+SABA+ipra)					
Heterogeneity: Tau^2=0; Chi^2=9.76, df=1(P=0); I^2=89.75%					
Test for overall effect: Z=1.38(P=0.17)					
Test for subgroup differences: Chi^2=2.77, df=1 (P=0.1), I^2=63.92%					



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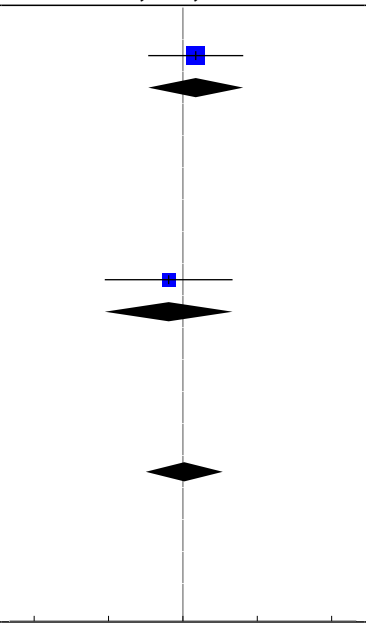
Analysis 1.16. Comparison 1 $MgSO_4$ + SABA + ipratropium versus SABA + ipratropium, Outcome 16 Adverse event: flushing.

Study or subgroup	MgSO4+SABA+ipra n/N	Placebo+SABA+ipra n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
1.16.1 Adults					
Goodacre 2013	3/332	2/358		57.61%	0[-0.01,0.02]
Subtotal (95% CI)	**332**	**358**		**57.61%**	**0[-0.01,0.02]**
Total events: 3 (MgSO4+SABA+ipra), 2 (Placebo+SABA+ipra)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.53(P=0.6)					
1.16.2 Children					
Powell 2013	2/252	3/255		42.39%	-0[-0.02,0.01]
Subtotal (95% CI)	**252**	**255**		**42.39%**	**-0[-0.02,0.01]**
Total events: 2 (MgSO4+SABA+ipra), 3 (Placebo+SABA+ipra)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.44(P=0.66)					
Total (95% CI)	**584**	**613**		**100%**	**0[-0.01,0.01]**
Total events: 5 (MgSO4+SABA+ipra), 5 (Placebo+SABA+ipra)					
Heterogeneity: Tau²=0; Chi²=0.45, df=1(P=0.5); I²=0%					
Test for overall effect: Z=0.07(P=0.94)					
Test for subgroup differences: Chi²=0.44, df=1 (P=0.51), I²=0%					



Comparison 2. $MgSO_4$ + SABA versus SABA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pulmonary function % predicted FEV1	4	208	Mean Difference (IV, Fixed, 95% CI)	3.34 [-1.58, 8.26]
1.1 Adults	3	146	Mean Difference (IV, Fixed, 95% CI)	2.18 [-3.30, 7.67]
1.2 Children	1	62	Mean Difference (IV, Fixed, 95% CI)	8.10 [-3.03, 19.23]
2 % predicted FEV1: subgroup: severity	3	188	Mean Difference (IV, Fixed, 95% CI)	4.12 [-1.81, 10.06]
2.1 Severe (FEV1 <50% predicted)	1	52	Mean Difference (IV, Fixed, 95% CI)	9.90 [0.05, 19.75]
2.2 Moderate	2	136	Mean Difference (IV, Fixed, 95% CI)	0.84 [-6.59, 8.27]
3 Pulmonary function PEF L/min	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Adults	3	155	Mean Difference (IV, Fixed, 95% CI)	11.91 [-4.12, 27.95]
3.2 Children	1	80	Mean Difference (IV, Fixed, 95% CI)	11.90 [-6.86, 30.66]

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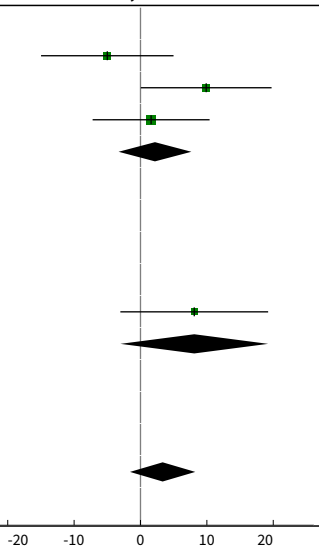
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Admission to hospital	6	375	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.52, 1.15]
4.1 Adults	4	213	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.45, 1.07]
4.2 Children	2	162	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.44, 2.98]
5 Heart rate at 120 mins	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Respiratory rate at 120 mins	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7 Diastolic blood pressure at 120 mins	2	120	Mean Difference (IV, Fixed, 95% CI)	0.72 [-1.35, 2.80]
8 Systolic blood pressure at 120 mins	2	120	Mean Difference (IV, Fixed, 95% CI)	0.89 [-2.69, 4.48]
9 Serious adverse events	5	243	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.04, 0.04]
9.1 Adults	4	181	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.04, 0.04]
9.2 Children	1	62	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.06, 0.06]
10 Any adverse events	5	694	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.05, 0.03]
10.1 Adults	4	329	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.10, 0.06]
10.2 Children	1	365	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.01]

Analysis 2.1. Comparison 2 $MgSO_4$ + SABA versus SABA, Outcome 1 Pulmonary function % predicted FEV1.

Study or subgroup	MgSO4 + SABA N	MgSO4 + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 Adults							
Bessmertny 2002	37	63 (21.9)	37	68 (21.9)		24.31%	-5[-14.98,4.98]
Hughes 2003	28	51.2 (17.3)	24	41.3 (18.7)		24.97%	9.9[0.05,19.75]
Sarhan 2016	10	51.2 (9.8)	10	49.6 (10.3)		31.18%	1.6[-7.21,10.41]
Subtotal ***	**75**		**71**			**80.46%**	**2.18[-3.3,7.67]**
Heterogeneity: Tau²=0; Chi²=4.37, df=2(P=0.11); I²=54.19%							
Test for overall effect: Z=0.78(P=0.44)							
2.1.2 Children							
Mahajan 2004	31	75.4 (26)	31	67.3 (18)		19.54%	8.1[-3.03,19.23]
Subtotal ***	**31**		**31**			**19.54%**	**8.1[-3.03,19.23]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.43(P=0.15)							
Total ***	**106**		**102**			**100%**	**3.34[-1.58,8.26]**
Heterogeneity: Tau²=0; Chi²=5.24, df=3(P=0.16); I²=42.74%							



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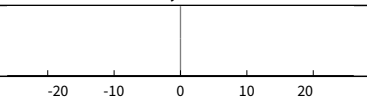
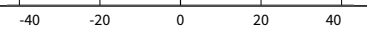
Study or subgroup	MgSO4 + SABA N	MgSO4 + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=1.33(P=0.18)							
Test for subgroup differences: Chi²=0.87, df=1 (P=0.35), I²=0%							



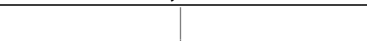
Analysis 2.2. Comparison 2 $MgSO_4$ + SABA versus SABA, Outcome 2 % predicted FEV1: subgroup: severity.

Study or subgroup	MgSO4 + SABA N	MgSO4 + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.2.1 Severe (FEV1 <50% predicted)							
Hughes 2003	28	51.2 (17.3)	24	41.3 (18.7)		36.28%	9.9[0.05,19.75]
Subtotal ***	**28**		**24**			**36.28%**	**9.9[0.05,19.75]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.97(P=0.05)							
2.2.2 Moderate							
Bessmertny 2002	37	63 (21.9)	37	68 (21.9)		35.33%	-5[-14.98,4.98]
Mahajan 2004	31	75.4 (26)	31	67.3 (18)		28.39%	8.1[-3.03,19.23]
Subtotal ***	**68**		**68**			**63.72%**	**0.84[-6.59,8.27]**
Heterogeneity: Tau²=0; Chi²=2.95, df=1(P=0.09); I²=66.1%							
Test for overall effect: Z=0.22(P=0.83)							
Total ***	**96**		**92**			**100%**	**4.12[-1.81,10.06]**
Heterogeneity: Tau²=0; Chi²=5.02, df=2(P=0.08); I²=60.18%							
Test for overall effect: Z=1.36(P=0.17)							
Test for subgroup differences: Chi²=2.07, df=1 (P=0.15), I²=51.76%							



Analysis 2.3. Comparison 2 $MgSO_4$ + SABA versus SABA, Outcome 3 Pulmonary function PEF L/min.

Study or subgroup	MgSO4 + SABA N	MgSO4 + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.3.1 Adults							
Aggarwal 2006	50	172.4 (43.7)	50	168.2 (54.6)		68.42%	4.2[-15.18,23.58]
Nannini 2000	19	332 (119)	16	282 (107)		4.58%	50[-24.91,124.91]
Sarhan 2016	10	92 (26.9)	10	67 (41.9)		27%	25[-5.86,55.86]
Subtotal ***	**79**		**76**			**100%**	**11.91[-4.12,27.95]**
Heterogeneity: Tau²=0; Chi²=2.29, df=2(P=0.32); I²=12.74%							
Test for overall effect: Z=1.46(P=0.15)							
2.3.2 Children							
Mohammedzadeh 2014	40	155.4 (46.9)	40	143.5 (38.3)		100%	11.9[-6.86,30.66]
Subtotal ***	**40**		**40**			**100%**	**11.9[-6.86,30.66]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.24(P=0.21)							



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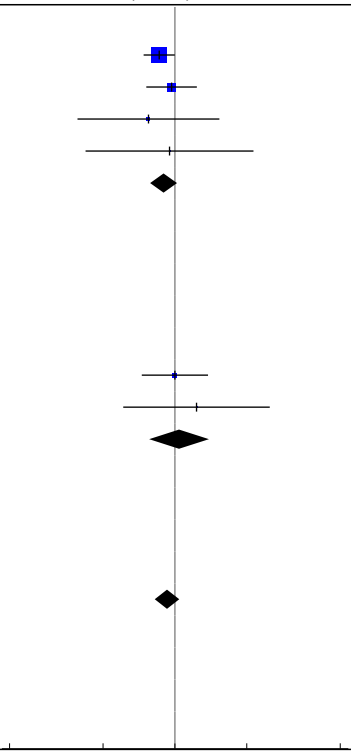
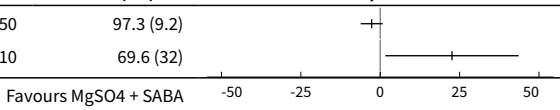
Analysis 2.4. Comparison 2 $MgSO_4$ + SABA versus SABA, Outcome 4 Admission to hospital.

Study or subgroup	MgSO4 + SABA n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Adults					
Hughes 2003	12/28	17/24		47.49%	0.61[0.37,1]
Aggarwal 2006	9/50	10/50		25.94%	0.9[0.4,2.02]
Kokturk 2005	1/14	2/12		5.59%	0.43[0.04,4.16]
Nannini 2000	1/19	1/16		2.82%	0.84[0.06,12.42]
Subtotal (95% CI)	**111**	**102**		**81.84%**	**0.69[0.45,1.07]**
Total events: 23 (MgSO4 + SABA), 30 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=0.88, df=3(P=0.83); I^2=0%					
Test for overall effect: Z=1.67(P=0.1)					
2.4.2 Children					
Turker 2017	6/50	6/50		15.57%	1[0.35,2.89]
Mahajan 2004	2/31	1/31		2.59%	2[0.19,20.93]
Subtotal (95% CI)	**81**	**81**		**18.16%**	**1.14[0.44,2.98]**
Total events: 8 (MgSO4 + SABA), 7 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=0.27(P=0.79)					
Total (95% CI)	**192**	**183**		**100%**	**0.78[0.52,1.15]**
Total events: 31 (MgSO4 + SABA), 37 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=2.19, df=5(P=0.82); I^2=0%					
Test for overall effect: Z=1.26(P=0.21)					
Test for subgroup differences: Chi^2=0.86, df=1 (P=0.35), I^2=0%					



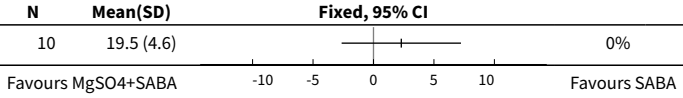
Analysis 2.5. Comparison 2 $MgSO_4$ + SABA versus SABA, Outcome 5 Heart rate at 120 mins.

Study or subgroup	MgSO4 + SABA N	MgSO4 + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Aggarwal 2006	50	94.6 (8.4)	50	97.3 (9.2)		-2.7[-6.15,0.75]
Sarhan 2016	10	92.2 (11.1)	10	69.6 (32)		22.6[1.61,43.59]



Analysis 2.6. Comparison 2 $MgSO_4$ + SABA versus SABA, Outcome 6 Respiratory rate at 120 mins.

Study or subgroup	MgSO4 + SABA N	MgSO4 + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Sarhan 2016	10	21.8 (6.5)	10	19.5 (4.6)		0%	2.3[-2.64,7.24]



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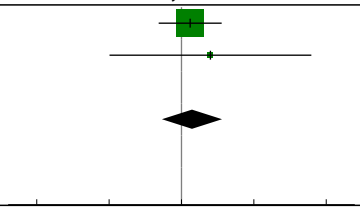
Analysis 2.7. Comparison 2 $MgSO_4$ + SABA versus SABA, Outcome 7 Diastolic blood pressure at 120 mins.

Study or subgroup	MgSO4 + SABA N	MgSO4 + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Aggarwal 2006	50	89.3 (5.5)	50	88.7 (5.6)		91.13%	0.6[-1.58,2.78]
Sarhan 2016	10	79 (7.7)	10	77 (8.2)		8.87%	2[-4.97,8.97]
Total ***	**60**		**60**			**100%**	**0.72[-1.35,2.8]**

Heterogeneity: Tau²=0; Chi²=0.14, df=1(P=0.71); I²=0%

Test for overall effect: Z=0.68(P=0.49)

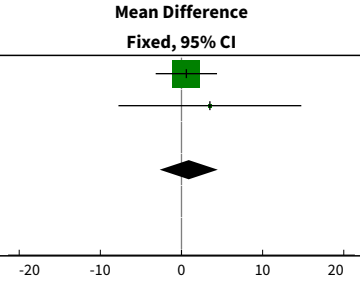


Analysis 2.8. Comparison 2 $MgSO_4$ + SABA versus SABA, Outcome 8 Systolic blood pressure at 120 mins.

Study or subgroup	MgSO4 + SABA N	MgSO4 + SABA Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Aggarwal 2006	50	138.8 (8.7)	50	138.2 (10.5)		89.89%	0.6[-3.18,4.38]
Sarhan 2016	10	114.5 (12.5)	10	111 (13.2)		10.11%	3.5[-7.77,14.77]
Total ***	**60**		**60**			**100%**	**0.89[-2.69,4.48]**

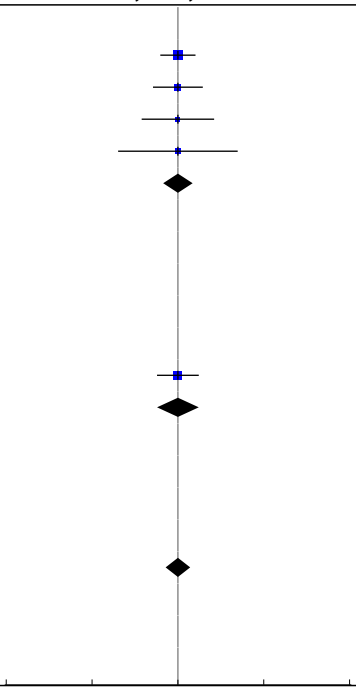
Heterogeneity: Tau²=0; Chi²=0.23, df=1(P=0.63); I²=0%

Test for overall effect: Z=0.49(P=0.63)



Analysis 2.9. Comparison 2 $MgSO_4$ + SABA versus SABA, Outcome 9 Serious adverse events.

Study or subgroup	MgSO4 + SABA n/N	SABA n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
2.9.1 Adults					
Bessmertny 2002	0/37	0/37		30.52%	0[-0.05,0.05]
Hughes 2003	0/28	0/24		21.32%	0[-0.07,0.07]
Nannini 2000	0/19	0/16		14.33%	0[-0.11,0.11]
Sarhan 2016	0/10	0/10		8.25%	0[-0.17,0.17]
Subtotal (95% CI)	**94**	**87**		**74.43%**	**0[-0.04,0.04]**
Total events: 0 (MgSO4 + SABA), 0 (SABA)					
Heterogeneity: Tau²=0; Chi²=0, df=3(P=1); I²=0%					
Test for overall effect: Not applicable					
2.9.2 Children					
Mahajan 2004	0/31	0/31		25.57%	0[-0.06,0.06]
Subtotal (95% CI)	**31**	**31**		**25.57%**	**0[-0.06,0.06]**
Total events: 0 (MgSO4 + SABA), 0 (SABA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**125**	**118**		**100%**	**0[-0.04,0.04]**
Total events: 0 (MgSO4 + SABA), 0 (SABA)					
Heterogeneity: Tau²=0; Chi²=0, df=4(P=1); I²=0%					
Test for overall effect: Not applicable					



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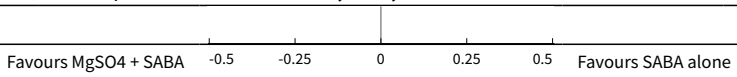
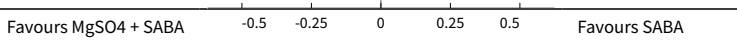
Study or subgroup	MgSO4 + SABA n/N	SABA n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Test for subgroup differences: Not applicable					



Analysis 2.10. Comparison 2 $MgSO_4$ + SABA versus SABA, Outcome 10 Any adverse events.

Study or subgroup	MgSO4 + SABA n/N	SABA n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
2.10.1 Adults					
Aggarwal 2006	20/50	18/50		14.43%	0.04[-0.15,0.23]
Ahmed 2013	0/60	0/60		17.32%	0[-0.03,0.03]
Bessmertny 2002	11/37	16/37		10.68%	-0.14[-0.35,0.08]
Nannini 2000	0/19	0/16		5.01%	0[-0.11,0.11]
Subtotal (95% CI)	**166**	**163**		**47.44%**	**-0.02[-0.1,0.06]**
Total events: 31 (MgSO4 + SABA), 34 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=2.84, df=3(P=0.42); I^2=0%					
Test for overall effect: Z=0.46(P=0.64)					
2.10.2 Children					
Alansari 2015	1/191	2/174		52.56%	-0.01[-0.03,0.01]
Subtotal (95% CI)	**191**	**174**		**52.56%**	**-0.01[-0.03,0.01]**
Total events: 1 (MgSO4 + SABA), 2 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.65(P=0.52)					
Total (95% CI)	**357**	**337**		**100%**	**-0.01[-0.05,0.03]**
Total events: 32 (MgSO4 + SABA), 36 (SABA)					
Heterogeneity: Tau^2=0; Chi^2=2.46, df=4(P=0.65); I^2=0%					
Test for overall effect: Z=0.61(P=0.54)					
Test for subgroup differences: Chi^2=0.09, df=1 (P=0.77), I^2=0%					



Comparison 3. $MgSO_4$ versus SABA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical severity score	3	93	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.62, 0.36]
1.1 Fischl index final score (120 mins)	1	33	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-1.07, 0.41]
1.2 Fischl index score (time point unclear)	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.11, 0.71]
1.3 Change in Fischl index at 120 mins	1	20	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.67, 1.27]
2 Admission to hospital	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

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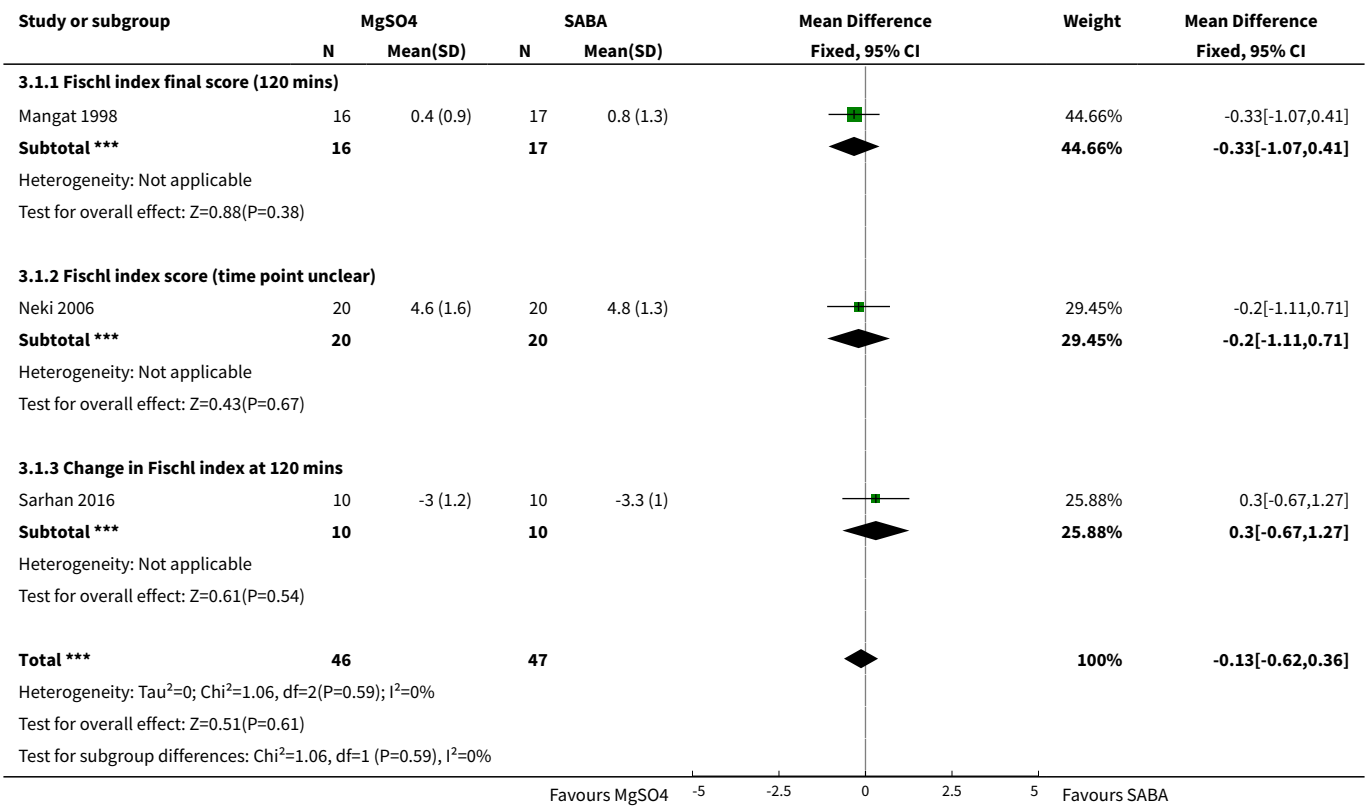
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Heart rate (120 mins)	1	20	Mean Difference (IV, Fixed, 95% CI)	21.20 [0.17, 42.23]
4 Respiratory rate	2	60	Mean Difference (IV, Fixed, 95% CI)	-2.40 [-3.91, -0.89]
5 Systolic pressure (120 mins)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6 Diastolic pressure (120 mins)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7 Serious adverse events	2	53	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.10, 0.10]
8 Mild-Moderate Side Effects	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 $MgSO_4$ versus SABA, Outcome 1 Clinical severity score.



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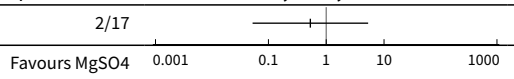
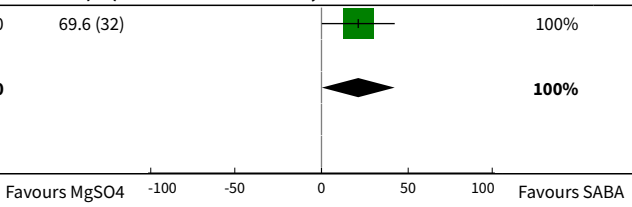
Analysis 3.2. Comparison 3 $MgSO_4$ versus SABA, Outcome 2 Admission to hospital.

Study or subgroup	MgSO4 n/N	SABA n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Mangat 1998	1/16	2/17		0.53[0.05,5.31]



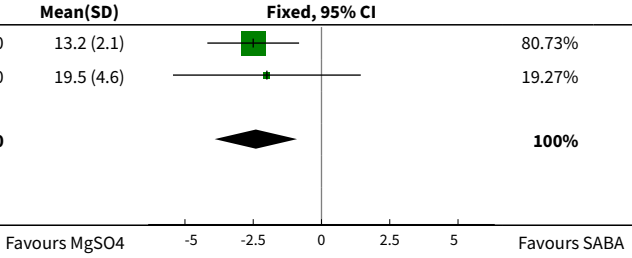
Analysis 3.3. Comparison 3 $MgSO_4$ versus SABA, Outcome 3 Heart rate (120 mins).

Study or subgroup	MgSO4 N	MgSO4 Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Sarhan 2016	10	90.8 (11.3)	10	69.6 (32)		100%	21.2[0.17,42.23]
Total ***	**10**		**10**			**100%**	**21.2[0.17,42.23]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.98(P=0.05)							



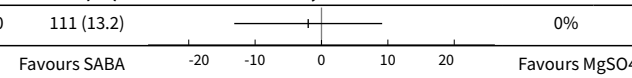
Analysis 3.4. Comparison 3 $MgSO_4$ versus SABA, Outcome 4 Respiratory rate.

Study or subgroup	MgSO4 N	MgSO4 Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Neki 2006	20	10.7 (3.2)	20	13.2 (2.1)		80.73%	-2.5[-4.18,-0.82]
Sarhan 2016	10	17.5 (3.1)	10	19.5 (4.6)		19.27%	-2[-5.44,1.44]
Total ***	**30**		**30**			**100%**	**-2.4[-3.91,-0.89]**
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.8); I^2=0%							
Test for overall effect: Z=3.12(P=0)							



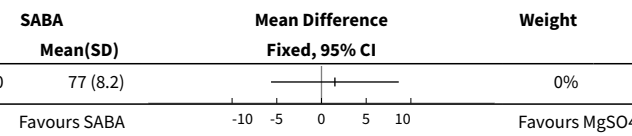
Analysis 3.5. Comparison 3 $MgSO_4$ versus SABA, Outcome 5 Systolic pressure (120 mins).

Study or subgroup	MgSO4 N	MgSO4 Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Sarhan 2016	10	109 (12.2)	10	111 (13.2)		0%	-2[-13.14,9.14]



Analysis 3.6. Comparison 3 $MgSO_4$ versus SABA, Outcome 6 Diastolic pressure (120 mins).

Study or subgroup	MgSO4 N	MgSO4 Mean(SD)	SABA N	SABA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Sarhan 2016	10	78.5 (8.1)	10	77 (8.2)		0%	1.5[-5.64,8.64]



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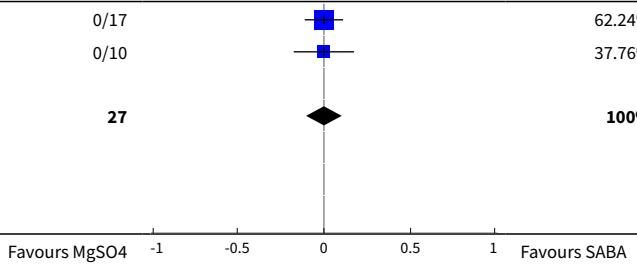
Analysis 3.7. Comparison 3 $MgSO_4$ versus SABA, Outcome 7 Serious adverse events.

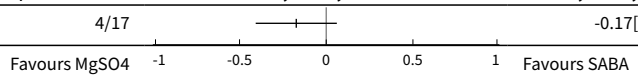
Study or subgroup	MgSO4 n/N	SABA n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Mangat 1998	0/16	0/17		62.24%	0[-0.11,0.11]
Sarhan 2016	0/10	0/10		37.76%	0[-0.17,0.17]
Total (95% CI)	**26**	**27**		**100%**	**0[-0.1,0.1]**

Total events: 0 (MgSO4), 0 (SABA)
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%
Test for overall effect: Not applicable



Analysis 3.8. Comparison 3 $MgSO_4$ versus SABA, Outcome 8 Mild-Moderate Side Effects.

Study or subgroup	MgSO4 n/N	SABA n/N	Risk Difference M-H, Fixed, 95% CI	Risk Difference M-H, Fixed, 95% CI
Mangat 1998	1/16	4/17		-0.17[-0.41,0.06]



ADDITIONAL TABLES

Table 1. Summary of Severity

Study	Severity of asthma exacerbation	Diagnosis based on	Population (adult/mixed/paediatric)
$MgSO_4$ and SABA and Ipratropium bromide versus SABA and Ipratropium			
Ashtekar 2008	Severe	BTS definition clinical features	Paediatric (2 to 16)
Drobina 2006	Unclear	PEF and clinical signs	Adults
Gallegos-Solórzano 2010	Moderate to severe	FEV1 < 60%	Adults >18
Gaur 2008	Severe	FEV1 < 30%	Adults (18 to 60)
Goodacre 2013	Severe	BTS definition	Adult (≥ 16)
Hossein 2016	Moderate to severe	PEF < 70% and clinical signs	Adult (> 16)
Powell 2013	Severe after conventional treatment	BTS definition	Paediatric (2 to 16)
MgSO4 and SABA versus SABA			
Abreu-Gonzalez 2002	Moderate	FEV1 and PEF at baseline	Adults

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Table 1. Summary of Severity *(Continued)*

Aggarwal 2006	Severe and life threatening	BTS definition clinical features and PEF	Mixed (13 to 60)
Ahmed 2013	Severe	PEF	Not documented
Alansari 2015	Moderate to severe	Clinical score	Paediatric (2 to 14)
Badawy 2014	Unclear	N/A	Adult
Bessmertny 2002	Moderate to severe	PEF between 40% to 80%	Adults (18 to 65)
Dadhich 2005	Severe	PEF < 50%	Adults
Hughes 2003	Severe	FEV1 < 50%	Adults (16 to 65)
Khashabi 2008	Unclear	Clinically defined as respiratory distress	Paediatric (mean age 3.55 years)
Kokturk 2005	Moderate to severe	Clinical scores and PEF	Adults (18 to 60)
Mahajan 2004	Moderate to severe	FEV1 between 45% and 75%	Paediatric (5 to 17)
Mohammedzadeh 2014	Moderate to severe	GINA definition	Paediatric (5 to 14)
Nannini 2000	Severe	PEF < 50%	Adult (> 18)
Sarhan 2016	Unclear	PEF < 300L/min	Mixed (11 to 70)
Turker 2017	Moderate	Not described	Children (3 to 15)
$MgSO_4$ versus SABA			
Dadhich 2005	Severe	PEF < 50%	Adults
Mangat 1998	Moderate to severe	PEF < 300 L/Min	Mixed (12 to 60)
Meral 1996	Moderate to severe	PEF < 75%	Paediatric
Neki 2006	Severe	FEV1 < 40% or PEF < 300 L/Min	Adult (15 to 60)
Sarhan 2016	Unclear	PEF < 300L/min	Mixed (11 to 70)

BTS: British Thoracic Society
GINA: Global Initiative for Asthma
FEV1: Forced expiratory volume in one second
PEF: Peak Expiratory Flow Rate

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Table 2. Summary of Characteristics of the studies – where patients were recruited from, additional treatment, exclusion criteria and side effects.

Study	Presentation to which department?	Origin	Primary outcome(s)	Total n randomised	Side effects (patients in study)	Pharmaceutical exclusions	Other Interventions
$MgSO_4$ and SABA and Ipratropium bromide versus SABA and Ipratropium							
Ashtekar 2008	Children's Assessment Unit after GP referral	Cardiff, Wales	ASS (Yung)	17	1 tingling in fingers and 1 transient hypotension	None stated	All management followed the BTS/SIGN guidelines; all children received 2 mg/kg prednisolone
Drobina 2006	ED	USA	PEF, admissions	110	No comment on side effects in paper	Not stated	All subjects received 50 mg of oral prednisone at the onset of the treatment
Gallegos-Solórzano 2010	ED	Mexico City, Mexico	% change FEV1, O_2 post treatment, admission rates	112	Dry and bitter mouth ($MgSO_4$ group 1), dizziness ($MgSO_4$ 1; placebo 1)	Use of steroids prior to presentation	All participants received one IV dose of 125 mg methylprednisolone at admission and 1 mg/kg/day for 10 days prednisolone,on discharge. Other treatments were administered according to the treating physician
Gaur 2008	ED	Delhi, India	FEV1	60	None reported	None stated	All participants received IV hydrocortisone on arrival
Goodacre 2013	ED	UK	Admission within 7d, visual analogue scale for breathlessness at 2 h	703	AEs (41 $MgSO_4$/salbutamol; 36 placebo/salbutamol)	$MgSO_4$ in the past 24 h	All participants were managed according to BTS/SIGN guidelines (consisting of oxygen, nebulised salbutamol (5 mg), nebulised ipratropium (500 µg), and oral prednisolone administered during recruitment, followed by up to 5 mg salbutamol added to each trial nebuliser. Other treatments were provided at the discretion of the clinician
Hossein 2016	ED	Tehran, Iran	PEFR improvement, admission rate	50	No serious side effects reported	None stated	All participants received 50 mg oral prednisolone
Powell 2013	ED and children's assessment units	UK	Yung asthma severity score	508	47 in $MgSO_4$ group and 59 in control group	None	Hospital-defined conventional treatment

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Table 2. Summary of Characteristics of the studies – where patients were recruited from, additional treatment, exclusion criteria and side effects *(Continued)*

MgSO4 and SABA versus SABA

Abreu-Gonzalez 2002	-	Tenerife Spain	FEV1, PEF	24	None reported	None stated	Not stated
Aggarwal 2006	ED	New Delhi India	PEF	100	Palpitations ($MgSO_4$/salbutamol 13; salbutamol/placebo 11) and tremors (7; 7).	None stated	Clinicians free to administer steroids, salbutamol, IV hydrocortisone if judged to be required
Ahmed 2013	-	Mymensingh, Bangladesh	PEF	120	None reported	None stated	Not stated
Alansari 2015	Paediatric emergency centre	Doha, Qatar	Time to readiness for discharge	400	Chest tightness and facial rash ($MgSO_4$/salbutamol 191), excessive cough (placebo/salbutamol 174)	None stated	All participants received methylprednisolone 1 mg/kg IV every 12h and additional nebulised albuterol at clinicians' discretion
Badawy 2014	Outpatient department and ED	Sohag, Egypt	Exacerbations post intervention, delivery outcome, postpartum health status	60	None reported	None stated	All participants received 100 mg hydrocortisone IV, 500 mg aminophylline IV
Bessmertny 2002	ED	Brooklyn, USA	FEV1 (% pred)	74	No SAEs reported	No theophylline or anticholinergics 2 h prior to presentation	Intravenous hydrocortisone, 2 mg/kg every 6 h, was administered to patients who failed to show an adequate improvement of pulmonary function after 3 initial doses of albuterol
Dadhich 2005	ED	Ajmer India	PEF	71	"Side effects were self limiting"	Not stated	Not stated
Hughes 2003	ED	Wellington New Zealand	FEV1	52	None reported	None	All participants received 100 mg hydrocortisone IV
Khashabi 2008	-	Urmia, Iran	Reduced mean duration of O_2 therapy in $MgSO_4$ group,	40	No side effects	Not stated	Not stated

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Table 2. Summary of Characteristics of the studies – where patients were recruited from, additional treatment, exclusion criteria and side effects. *(Continued)*

			no change in Respiratory Distress Score)				
Kokturk 2005	ED	Gazi, Turkey	PEF difference	26	Transient hypotension (1 $MgSO_4$), palpitation (1 salbutamol)	None	All participants received 1 mg/kg prednisolone. Theophylline, anticholinergics and salbutamol given at clinicians discretion
Mahajan 2004	ED	Detroit, USA	% change in FEV1	62	No side effects	Steroids, ipratropium or theophylline in the last 3 days.	All participants received 2 mg/kg of prednisone
Mohammedzadeh 2014	-	Babol, Iran	Pulmonary index, PEFR, adjusted PEFR	80	-	Corticosteroids; steroids, theophylline or ipratropium use within last 72 h	Not stated
Nannini 2000	ED	4 hospitals in Argentina	PEF, admissions	35	None reported	Oral or parenteral steroids in the last 7 days	No other medications were permitted during the study except supplemental oxygen; if the patient's condition worsened, a 2.5 mg dose of nebulized salbutamol was administered at the discretion of the treating physician
Sarhan 2016	Chest and ED	Minia, Egypt	Clinical improvement, PEFR	30	None severe enough to warrant withdrawal	Bronchodilators in last 6 h, steroids in last 12 h	Nebulised salbutamol, IV hydrocortisone, IV aminophylline at clinicians' discretion
Turker 2017	ED	Turkey	Modified pulmonary index score	100	"No side effect caused by magnesium was observed in any of the patients in the study"	Not stated	Nebulised salbutamol (0.15 mg/kg), methylprednisolone 1 mg/kg IV; Oxygen was given to patients with SaO2≤ 95%
$MgSO_4$ versus SABA							
Dadhich 2005	ED	Ajmer India	PEF	71	"Side effects were self limiting"	Not stated	Not stated

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Table 2. Summary of Characteristics of the studies – where patients were recruited from, additional treatment, exclusion criteria and side effects. *(Continued)*

Mangat 1998	ED	St John's College, India	PEF, Fischl index score, admissions	33	Transient self limiting hypotension (1) palpitation (1) tremors (2) all in control group and only 1 transient hypotension in $MgSO_4$ group (33)	Oral parenteral bronchodilators (6 h) steroids (last 12 h)	All participants received 100 mg hydrocortisone IV
Meral 1996	-	Izmir, Turkey	% change in PEF ASS (Davies Leffert, Dabbous score)	40	No side effects	Beta2-agonists or theophylline in the last 12 h	No other medication given
Neki 2006	-	Amritsar Punjab	PEF, RR, Fischl index	40	-	Oral, inhaled or parenteral steroids in last 12 h	All participants received 100 mg hydrocortisone IV
Sarhan 2016	Chest and ED	Minia, Egypt	Clinical improvement, PEFR	30	None severe enough to warrant withdrawal	Bronchodilators in last 6 h, steroids in last 12 h	Nebulised salbutamol, IV hydrocortisone, IV aminophylline at clinicians' discretion

ASS: Asthma Severity Score; BP: blood pressure; ED: emergency department; FEV1: Forced expiratory volume in 1 second; h: hour(s)
HR: heart rate; IV: intravenous; $MgSO_4$: magnesium sulfate; PEF: Peak Expiratory Flow Rate; SAEs: serious adverse events

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Table 3. Summary of Interventions

Study (N)	Magnesium sulfate			Control		
	Dose	N	Co-interventions	Dose	N	Co-interventions
$MgSO_4$ and SABA and Ipratropium bromide versus SABA and Ipratropium						
Ashtekar 2008	2.5 mL isotonic $MgSO_4$ (151 mg /dose)	7	500 mcg Ipratropium bromide 2.5 mg salbutamol or 5 mg salbutamol (depending on age) 3 times per h	2.5 mL of isotonic saline)	10	Same as for $MgSO_4$ group
Drobina 2006	150 mg $MgSO_4$ (0.3 mL of 50% $MgSO_4$ heptahydrate)	60	Albuterol sulfate (0.5%) 5 mg/mL) and 0.5 mg ipratropium bromide (0.02% inhalation solution) (frequency*)	No placebo so volume will be less: i.e. blinding may be an issue)	50	Same as for $MgSO_4$ group
Gallegos-Solórzano 2010	3 mL (333 mg) of 10% isotonic $MgSO_4$ (1 g/10 mL)	60 (30 withdrawals)	2.5 mg albuterol and 500 mcg ipratropium 3 doses per hour	3 mL isotonic saline	52 (22 withdrawals)	Same as for $MgSO_4$ group
Gaur 2008	3 mL (3.2 g%) isotonic $MgSO_4$	30	Salbutamol and ipratropium (dose*, frequency*)	Saline	30	Same as for $MgSO_4$ group
Goodacre 2013	2 mmol $MgSO_4$	339 (7 withdrawal)	7.5 mL 0.9% NaCl nebulised, 3 doses; 100 mL 0.9% NaCl IV once, BTS/SIGN standard treatments plus others at clinicians' discretion	7.5 mL 0.9% saline nebulised, 3 doses, 100 mL 0.9% NaCl IV once	364 (7 withdrawal)	BTS/SIGN standard treatments plus others at clinicians' discretion
Hossein 2016	3 mL (260 mmol/L) MgSO4	25	2.5 mg salbutamol, 0.5 mg ipratropium nebulised every 20 to 60 minutes, 50 mg oral prednisolone (once*)	3 mL 0.9% NaCl	25	Same as for $MgSO_4$ group
Powell 2013	2.5 mL 250 mmol/L $MgSO_4$	252 (13 withdrawals)	3 doses every 20 min. Hospital-defined conventional treatment	2.5 mL isotonic saline	256 (10 withdrawals)	Same as for $MgSO_4$ group
MgSO4 and SABA versus SABA						
Abreu-Gonzalez 2002	2 mL $MgSO_4$ (isotonic)	13	400 mcg salbutamol (once*)	2 mL of a physiological serum of an inhaled form 11 patients	11	400 mcg salbutamol
Aggarwal 2006	1 mL of 500 mg/mL $MgSO_4$	50	1 mL salbutamol (dose*, 8 mL distilled water, (295 mOsml/kg) 3 times per h	7.5 mL normal saline	50	1 mL salbutamol (dose*),

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Table 3. Summary of Interventions *(Continued)*

			ultrasonic nebuliser			1.5 mL distilled water (287 mOsml/kg) 3 times per h
Ahmed 2013	$MgSO_4$ (dose* frequency*)	60	Not recorded	Normal saline (dose* frequency*)	60	Not recorded
Alansari 2015	800 mg (15 mL) $MgSO_4$	208 (17 withdrawals)	5 mg albuterol, divided into 3 doses over 1 h. Methylprednisolone 1 mg/kg IV every 12 h. 3 doses nebulized 1 mL albuterol (5 mg/mL), 250 mcg ipratropium, 2 mL normal saline before trial doses started	15 mL 0.9% NaCl	192 (18 withdrawals)	Same as for $MgSO_4$ group
Badawy 2014	500 mg (1mL) $MgSO_4$	30	1 mL salbutamol solution (dose*), 8 mL 0.9% NaCl, max 3 doses with 20 mins apart. 100 mg hydrocortisone IV, 500 mg aminophylline IV (once*)	1 mL 0.9% NaCl	30	Same as for $MgSO_4$ group
Bessmertny 2002	$MgSO_4$ (384 mg)	37 (3 withdrawals)	Followed by (i.e. not mixed) albuterol 2.5 mg/mL 3 times per h	Normal saline (no volume documented)	37 (3 withdrawals)	Same as for $MgSO_4$ group
Dadhich 2005	$MgSO_4$	26	No doses in any group or co-interventions described	Not stated	24	No doses in any group or co-interventions described
Hughes 2003	2.5 mL isotonic $MgSO_4$ (250 mmol/L 151 mg) 28 patients	28	2.5 mg salbutamol 3 times per 30 minutes	2.5 mL normal saline	24	Same as for $MgSO_4$ group
Khashabi 2008	Isotonic $MgSO_4$ (dose*, frequency*)	*	Salbutamol (dose*)	2.5 mL normal saline (frequency*)	*	Same as for $MgSO_4$ group
Kokturk 2005	Isotonic $MgSO_4$ (2.5 mL)	14	Salbutamol (dose*) 3 times per h then 1 per h for 3 h	2.5 mL normal saline	12	Same as for $MgSO_4$ group
Mohammedzadeh 2014	3 mL 7.5% $MgSO_4$	40	0.15 mg/kg salbutamol 3 doses, every 20 min	3 mL normal saline	40	Same as for $MgSO_4$ group
Mahajan 2004	2.5 mL Isotonic (6.3%) $MgSO_4$ solution	31	Albuterol 2.5 mg 1 dose	2.5 mL normal saline	31	Same as for $MgSO_4$ group

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Table 3. Summary of Interventions *(Continued)*

Nannini 2000	3 mL isotonic $MgSO_4$ (286 mOsml, 7.5%, 225 mg)	19	0.5 mL 2.5 mg salbutamol 1 dose*	3 mL normal saline	16	Same as for $MgSO_4$ group
Sarhan 2016	2.5 mL MgSO4 (100 mg), 0.5 mL salbutamol (2.5 mg)	10	4 doses at 20 min intervals. If needed: additional nebulised salbutamol, IV hydrocortisone, IV aminophylline	2.5 mL isotonic saline	10	Same as for MgSO4 group
Turker 2017	1 mL magnesium sulfate (15%) + 1.5 mL isotonic saline	50	3 doses at 20 min intervals. Also nebulised salbutamol (0.15 mg/kg), methylprednisolone 1 mg/kg IV; Oxygen was given to patients with SaO2 ≤ 95%	1.5 mL isotonic saline	50	Same as for $MgSO_4$ group
$MgSO_4$ versus SABA						
Dadhich 2005	$MgSO_4$	21	No doses in any group or co-interventions described	Not stated	24	No doses in any group or co-interventions described
Mangat 1998	3.2% solution $MgSO_4$ = 95 mg)	16	4 doses every 20 minutes	3 mL (2.5 mg) salbutamol	17	Four doses every 20 minutes
Meral 1996	2 mL $MgSO_4$ (280 mmol/L)	20	1* dose given over 10 to 15 minutes	Salbutamol 2.5 mg in 2.5 mL	20	1 dose* given over 10 to 15 minutes
Neki 2006	20 patients 3.2 G % $MgSO_4$	20	4 doses every 20 min	3 mL of 25 mg* salbutamol (likely decimal point missing)	20	Same as for MgSO4 group
Sarhan 2016	3 mL (100 mg) MgSO4	10	4 doses at 20 min intervals. If needed: additional nebulised salbutamol, IV hydrocortisone, IV aminophylline	0.5 mL salbutamol (2.5 mg)	10	Same as for $MgSO_4$ group
TOTAL: 2907 randomised to comparisons of interest. 130 withdrawn, 2777 completed		**TOTAL: 1476 randomised, 70 withdrawn = 1406 completed intervention**			**TOTAL: 1431 randomised, 60 withdrawn = 1371 completed control**	

* denotes uncertainty

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Table 4. Outcomes

Study ID (author, date of publication)	Review primary outcomes		Review secondary outcomes				
	FEV1	PEF	Clinical severity scores	Hospital admissions	Duration of symptoms	Vital signs	Adverse effects
$MgSO_4$ and SABA and Ipratropium bromide versus SABA and Ipratropium							
Ashtekar 2008	N	N	Y	N	N	N	Y
Drobina 2006	N	P	N	N	N	N	P
Gallegos-Solórzano 2010	Y	N	N	N	N	N	Y
Gaur 2008	Y	N	N	N	N	N	N
Goodacre 2013	N	Y	N	Y	N	Y	Y
Hossein 2016	N	Y	Y	Y	N	Y	N
Powell 2013	N	N	Y	P	N	N	Y
MgSO4 and SABA versus SABA							
Abreu-Gonzalez 2002	Y	Y	N	N	N	N	N
Aggarwal 2006	N	Y	N	Y	N	Y	Y
Ahmed 2013	N	P	N	N	N	N	N
Alansari 2015	N	N	Y	P	N	N	Y
Badawy 2014	Y	Y	N	N	N	Y	N
Bessmertny 2002	P	N	N	N	N	N	Y
Dadhich 2005	P	P	N	N	N	N	Y
Hughes 2003	Y	N	N	Y	N	N	Y
Khashabi 2008	N	N	N	N	N	N	N

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Table 4. Outcomes *(Continued)*

Kokturk 2005	N	Y	P	Y	N	N	Y
Mahajan 2004	Y	N	N	Y	N	N	Y
Mohammedzadeh 2014	N	Y	Y	N	N	N	N
Nannini 2000	N	Y	N	Y	N	N	Y
Sarhan 2016	N	Y	Y	N	N	Y	N
Turker 2017	N	N	Y	Y	N	N	Y
$MgSO_4$ versus SABA							
Dadhich 2005	P	P	N	N	N	N	Y
Mangat 1998	N	Y	N	Y	N	N	Y
Meral 1996	N	Y	N	N	N	N	Y
Neki 2006	N	Y	N	N	N	Y	N
Sarhan 2016	N	Y	Y	N	N	Y	N

N – the study did not report the outcome but it is not clear whether the outcome was measured or not
Y – full reporting
P – partial reporting

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APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
CENTRAL (*The Cochrane Library*)	Monthly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/

2. asthma$.mp.

3. (antiasthma$ or anti-asthma$).mp.

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4. Respiratory Sounds/

5. wheez$.mp.

6. Bronchial Spasm/

7. bronchospas$.mp.

8. (bronch$ adj3 spasm$).mp.

9. bronchoconstrict$.mp.

10. exp Bronchoconstriction/

11. (bronch$ adj3 constrict$).mp.

12. Bronchial Hyperreactivity/

13. Respiratory Hypersensitivity/

14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.

15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.

16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Appendix 2. Search strategies to identify relevant studies

Cochrane Airways Trials Register

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 magnesium*
#6 MgSO4
#7 #5 or #6
#8 #4 and #7

[In search line #1, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, asthma]

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ClinicalTrials.gov & WHO ICTRP

Search terms: magnesium and asthma

Study type: Interventional Studies

Appendix 3. Search methods for previous version of review (2005-2012)

Electronic searches

The Cochrane Airways Groups "Asthma and Wheez* RCT" register was searched for the following terms: magnesium OR MgSO4 OR Mg OR MS OR magnesium sulfate or magnesium sulphate. The results of this search were screened to omit studies that clearly involved only intravenous or parenteral administration of magnesium.

In addition, searches were also conducted on the following computerized bibliographic databases: MEDLINE (1966-2005), EMBASE (1988 to 2005), LILACS, Cochrane Clinical Trials Registry, Web of Science and Dissertation Abstracts.

WHAT'S NEW

Date	Event	Description
6 September 2017	New citation required and conclusions have changed	Nine new trials with 2051 participants were added to the 896 (16 trials) in the previous version of the review. We re-ordered the comparisons to reflect current asthma management. The evidence has been strengthened by the addition of several large well-conducted trials. We are more confident that the treatment is likely to be well tolerated; however, there remains uncertainty about modest benefits for lung function and hospital admission when added to standard therapies.
6 September 2017	New search has been performed	New literature search run and incorporated.

HISTORY

Protocol first published: Issue 1, 2004
Review first published: Issue 2, 2005

Date	Event	Description
28 September 2012	New citation required and conclusions have changed	Ten new trials with 600 participants added to the 296 in the previous version of the review. We added a new comparison of inhaled magnesium sulfate in addition to inhaled β_2 -agonist and ipratropium bromide. The evidence remains inconclusive, but whilst there is no good evidence that inhaled magnesium sulfate can be used as a substitute for inhaled beta$_2$-agonists, there is a suggestion of benefit in pulmonary function when used in addition to inhaled beta$_2$-agonists (with or without ipratropium) in severe asthma exacerbations.
28 September 2012	New search has been performed	New literature search run.
28 July 2008	Amended	Converted to new review format.
22 August 2005	New citation required and conclusions have changed	Substantive amendment

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CONTRIBUTIONS OF AUTHORS

For the 2017 update, RK and RN identified the included studies, extracted data, assessed risk of bias and analysed the data. RN and SM performed the GRADE assessments. RK and RN drafted the manuscript CP provided advice. All authors read and approved the final version for publication.

DECLARATIONS OF INTEREST

Drs. Hughes and Beasley were involved as Primary and Co-investigator on one of the trials included in this review (Hughes 2003). Dr Powell was a co-author of the pilot work completed in Ashtekar 2008 and was the chief investigator of the MAGNETIC study in children (Powell 2013). Dr Powell was not involved in the selection of studies for inclusion, data extraction, risk of bias assessment or GRADE assessments.

None of the other review authors has any known conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Department of Emergency Medicine, University of Alberta, Edmonton, AB, Canada.
- National Institute of Health Research (SJM), UK.

External sources

- Alberta Cancer Board, Canada.
- Canadian Institutes of Health Research (CIHR), Ottawa (BHR), Canada.
- Canadian Institutes of Health Research (CIHR), Ottawa, ON (BH Rowe),, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the 2012 update the 'Risk of bias' tool has been updated to that advised in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Three new review authors were added and the sensitivity analyses have been amended to investigating risk of bias rather than methodological quality.

In 2017 the following changes were made.

- Background, Results and Discussion substantially re-drafted.
- Comparisons re-ordered to reflect current clinical practice.
- We chose to present outcomes at, or as close to as possible, 60 minutes from baseline. This time point was decided by consensus.
- We performed a post-hoc sensitivity analysis excluding trials with unusually small standard deviations.
- We chose to exclude one study from the meta-analyses due to concerns about baseline imbalance and the narrow population recruited (pregnant women only) (Badawy 2014).
- We added a 'Summary of findings' table.
- Two review authors stepped down (Richard Beasley and Kerry Dwan) and two new authors were added (Rachel Knightly and Rebecca Normansell).

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Inhalation; Adrenergic beta-Agonists [*administration & dosage] [adverse effects]; Anti-Asthmatic Agents [*administration & dosage] [adverse effects]; Asthma [*drug therapy]; Bronchodilator Agents [administration & dosage]; Disease Progression; Drug Therapy, Combination [methods]; Hospitalization [statistics & numerical data]; Ipratropium [administration & dosage]; Magnesium Sulfate [*administration & dosage] [adverse effects]; Patient Readmission [statistics & numerical data]; Randomized Controlled Trials as Topic; Respiratory Function Tests

MeSH check words

Adult; Child; Humans

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